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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

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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 2021 to 24 February 2022. 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 Guideline on Good Pharmacovigilance Practices, guidance from the European Medicines Agency on the Consideration on Core Requirements for PSURs of coronavirus disease-2019 vaccines,[1] and guidance outlined in the European Medicines Agency's Consideration on Core Requirements for Risk Management Plans of coronavirus disease-2019 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 coronavirus disease-2019 in adults greater than or equal to 18 years of age. Ad26.COV2.S is supplied as a colourless to slightly yellow, clear to very opalescent single dose suspension for intramuscular injection. The indication is as listed in the Company Core Data Sheet and represents the broadest Company-supported use.

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. 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 Company Core Data Sheet.

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 injection (see Section 1, Introduction).

Worldwide Marketing Authorisation Status

Ad26.COV2.S is authorised or (conditionally) approved in 128 countries/territories worldwide (see Section 2, Worldwide Marketing Authorisation Status).

Exposure

Cumulative Exposure in Clinical Trials

Overall, an estimated 81,399 healthy participants have been enrolled in the Ad26.COV2.S clinical program, of which approximately 67,021 participants have received Ad26.COV2.S in the Company-sponsored interventional clinical trials. Of these, 580 participants were exposed to Ad26.COV2.S in the Phase 1 trials, 935 participants were exposed to Ad26.COV2.S in a Phase 1/2a trial, 1,554 participants were exposed to Ad26.COV2.S in the Phase 2 trials, 537 participants were exposed to Ad26.COV2.S in the Phase 2a trial, 109 participants were exposed to Ad26.COV2.S in the Phase 2/3 trial, and over

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

[2] EMA/PRAC/234052/2021 (dated 10 June 2021)

63,306 participants were exposed to Ad26.COV2.S in the Phase 3 trials (see Section 5.1, Cumulative Subject Exposure in Clinical Trials).

Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative

From launch to 28 February 2022, there were a total of 361,986,800 distributed doses and 44,105,710 administered doses of Ad26.COV2.S worldwide.

A total of 1,454,440 homologous Ad26.COV2.S booster doses were administered in South Korea and in the United States from launch to 28 February 2022.

Interval

From 01 September 2021 to 28 February 2022, there were a total of 283,450,700 distributed doses and 10,483,523 administered doses of Ad26.COV2.S worldwide.

A total of 1,454,432 homologous Ad26.COV2.S booster doses were administered in South Korea and in the US from 01 September 2021 to 28 February 2022 (see Section 5.2, Cumulative and Interval Patient Exposure From Marketing Experience).

Summary of the Overall Benefit-Risk Analysis Evaluation

Despite increasing numbers of vaccinated subjects, the ongoing severe acute respiratory syndrome coronavirus-2 pandemic remains a public health issue of international concern. The emergence of new virulent lineages has fuelled the need for highly effective preventative measures. Effective and safe coronavirus disease-2019 vaccines remain a pivotal tool for preventing the disease.

Ad26.COV2.S demonstrated high efficacy against severe/critical disease caused by severe acute respiratory syndrome coronavirus-2 and protection against hospitalisation and death in clinical trial settings. Analysis of spontaneous reports of vaccination failure did not show trends for lack of efficacy. Potential safety concerns will continue to be monitored.

As of 28 February 2022, over 44,105,710 doses of the Ad26.COV2.S vaccine have been administered worldwide. 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 indication of active immunisation to prevent coronavirus disease-2019 infection caused by severe acute respiratory syndrome coronavirus-2 in adults ≥18 years of age (see Section 18.2, Benefit-Risk Analysis Evaluation).

Actions Taken and Proposed for Safety Reasons

During this reporting period, several actions were taken for safety reasons in various regions. Details on the actions can be found in Appendix 1.1 (see Section 3, Actions Taken in the Reporting Interval for Safety Reasons, and Section 19, Conclusions and Actions).

Conclusions

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

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ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronyms/Abbreviations

AAV	Autoantibodies Associated Vasculitis
Ad26	Adenovirus Type 26
ADR	Adverse Drug Reaction
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AER	Adverse Event Report Number
AESI	Adverse Event of Special Interest
AIH	Autoimmune Hepatitis
AMN	Acute Macular Neuroretinopathy
AR	Adverse Reaction
BC	Brighton Collaboration
CBER	Center for Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Sciences
CLS	Capillary Leak Syndrome
cMA	Conditional Marketing Authorisation
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease-2019
CTs	Clinical Trials
CRP	C-Reactive Protein
cRMP	Core Risk Management Plan
CSR	Clinical Study Report
C-VIPER	COVID-19 Vaccines International Pregnancy Exposure Registry
CVACVST	Cerebrovascular Accident and StrokeCerebral Vein Sinus Thrombosis
CXCL4	Cationic Platelet Chemokine PF4
DHPC	Direct Healthcare Professional Communication
DIC	Disseminated Intravascular Coagulation
DLD	Data Lock Date
DLP	Data Lock Point
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic acid
DVT	Deep Vein Thrombosis
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EF	Ejection Fraction
EM	Erythema Multiforme
EMA	European Medicines Agency
EOI	Event(s) of Interest
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUA	Emergency Use Authorisation
EUPI	European Union Product Information
EU-RMP	European Union-Risk Management Plan
FAERS	Food and Drug Administration (United States) Adverse Event Reporting System
FAR	Final Assessment Report

FAS	Final Analyses Set
FDA	Food and Drug Administration (United States)
GBS	Guillain-Barre Syndrome
GD	Graves' disease
GMC	Geometric Mean Concentrations
GMR	Geometric Mean Ratios
GVP	Good Pharmacovigilance Practices
HCWs	Health care workers
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IBD	International Birth Date
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IgE	Immunoglobulin E
ITP	Immune Thrombocytopenia
IM	Intramuscular
LOE	Lack of Efficacy/Effectiveness
LL	Line Listing
KDCA	Korea Disease Control and Prevention Agency
MAAEs	Medically Attended Adverse Events
MAH	Marketing Authorisation Holder (Company)
MCD	Minimal Change Disease
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Related Coronavirus
MHRA	Medicine and Healthcare products Regulatory Agency
MI	Myocardial Infarction
MIS	Multisystem Inflammatory Syndrome
MMR-V	Measles Mumps, Rubella and Varicella
mRNA	Messenger Ribonucleic Acid
MSSR	Monthly Summary Safety Report
NHP	nonhuman primate(s)
NHS	National Health Service
NIH	National Institute of Health
O/E	Observed-to-Expected
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PF4	Anti-platelet factor 4
PI	Prescribing Information
PM	Post-marketing
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Reports
PT	Painless Thyroiditis
PT	Preferred Term (MedDRA)
PV	Pharmacovigilance
RMP	Risk Management Plan
ROW	Rest of World
RPGN	Rapidly Progressive Glomerulonephritis
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
RWE	Real World Evidence
S	Spike

SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SAT	Subacute Painful Thyroiditis
SCAR	Severe Cutaneous Adverse Reaction
SCCS	Self-Controlled Case Series
SMQ	Standardised MedDRA Query
SNHL	Sensorineural Hearing Loss
SOC	System Organ Class (MedDRA)
SPEP	Serum Protein Electrophoresis
SSR	Summary Safety Report
STeMS	Self-Service Text Mining Solution
TFUQs	Targeted Follow-Up Questionnaires
TST	Transverse Sinus Thrombosis
TTO	Time To Onset
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
US PVP	United States Pharmacovigilance Plan
VAED	Vaccine-associated Enhanced Disease
VAERD	Vaccine-associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VITT	Vaccine-induced Immune Thrombocytopenia
VOC	Variants of Concern
VOI	Variants Of Interest
VTE	Venous Thromboembolism
WHO	World Health Organisation

Definitions of Terms

Authorised product	A health authority has granted marketing authorisation for the active substance/ product and the licence is currently active. This may not include countries where the product is available via other means (e.g., 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 (e.g., new indications, dosage range, frequency, combinations) • Those that influence the freedom of choice for a specific treatment option by the treating health professional (e.g., 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.
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 medicinal product in an approved indication and includes any of the following as a primary objective: • To quantify potential or identified risks, e.g., 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 (e.g., 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 (e.g., 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 (e.g., distribution of the tools reaching the target population, assessing clinical knowledge, assessing clinical actions), refer to Guideline on Good Pharmacovigilance Practices (GVP) Module XVI-Guideline on risk minimisation measures: selection of tools and effectiveness indicators.
Source	Classification of reporter or case (e.g., 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 2021 to 24 February 2022. 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 (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. 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 adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein. Following vaccination, the S protein is expressed and stimulates an immune response. One dose of Ad26.COV2.S contains $5x10^{10}$ virus particles (vp) in 0.5 mL. Ad26.COV2.S is produced in the PER.C6® TetR Cell Line and by recombinant deoxyribonucleic acid (DNA) technology. Ad26.COV2.S contains genetically modified organisms. Information regarding the pharmacodynamic and pharmacokinetic properties is contained in the appended CCDS.

Ad26.COV2.S contains the following excipients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin, polysorbate-80, sodium chloride, sodium hydroxide, hydrochloric acid, and water for injections.

2. WORLDWIDE MARKETING AUTHORISATION STATUS

The IBD for Ad26.COV2.S is 25 February 2021 based on the first authorisation in Bahrain. The indications and the approved doses can be found in Section 1, Introduction. Ad26.COV2.S is authorised or (conditionally) approved in 128 countries/territories worldwide and Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organization (see Table 1).

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

[4] EMA/PRAC/234052/2021 (dated 10 June 2021)

Table 1: List of Countries/Territories (n=128)

Algeria	Comoros	Haiti	Malta	Saudi Arabia	Vietnam
Angola	Congo	Hungary	Mauretania	Sierra Leone	Zambia
Antigua and Barbuda	Congo, The Democratic Republic Of The	Iceland	Mauritius	Slovakia	Zimbabwe
Argentina	Cote D'Ivoire	India	Mexico	Slovenia	
Australia	Croatia	Indonesia	Moldova, Republic Of	Solomon Island	
Austria	Cyprus	Ireland	Mozambique	Somalia	
Bahamas	Czech Republic	Italy	Namibia	South Africa	
Bahrain	Denmark	Jamaica	Nepal	South Korea	
Bangladesh (WHO)	Djibouti	Jordan	Netherlands	South Sudan	
Belgium	Egypt	Kazakhstan	New Zealand	Spain	
Belize	Estonia	Kenya	Nicaragua	Sudan	
Benin	Eswatini	Kuwait	Niger	Sweden	
Bolivia	Ethiopia	Laos/Lao PDR	Nigeria	Switzerland	
Botswana	Finland	Latvia	Norway	Syrian Arab Republic	
Brazil	France	Lebanon	Oman	Tanzania	
Bulgaria	Gabon	Lesotho	Panama	Thailand	
Burkina Fasso	Gambia	Liberia	Papua New Guinea	Togo	
Burundi	Georgia	Libya	Peru	Trinidad and Tobago	
Cabo Verde	Germany	Liechtenstein	Philippines	Tunisia	
Cameroon	Ghana	Lithuania	Poland	Uganda	
Canada	Greece	Luxembourg	Portugal	Ukraine	
Central African Republic	Guatemala	Madagascar	Qatar	United Arab Emirates	
Chad	Guinea	Malawi	Romania	United Kingdom (Great Britain)	
Chile	Guinea-Bissau	Malaysia	Rwanda	United Kingdom (Northern Ireland)	
Colombia	Guyana	Mali	Sao Tome and Principe	United States	

Key: n=Number; PDR= People's' Democratic Republic.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

The significant actions taken for safety reasons during the period covered by this report are presented in Appendix 1.1.

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 11 February 2022. Significant changes to the CCDS (ie, CCSI) made within the reporting interval are listed in Table 2.

Table 2: Significant Changes to the Ad26.COV2.S CCDS During the Reporting Period

CCDS Version and Date	CCDS Section	Description of Change(s)
Version 8, 08 November 2021	Warnings and Precautions	Addition of text on ITP.
	Adverse Reactions	Addition of CLS as a post-marketing ADR.
Version 9, 18 November 2021	Dosage and Administration Adverse Reactions Clinical Efficacy Immunogenicity	Update to include homologous booster and heterologous booster for all sections listed.
Version 10, 30 November 2021	Contraindications	Contraindicated in individuals with a history of confirmed TTS following any COVID-19 vaccine.
	Warnings and Precautions	TTS subsection updated to include those individuals who have experienced TTS with any COVID-19 vaccine should not receive Janssen COVID-19 vaccine.
Version 11, 11 February 2022	Pregnancy, Breastfeeding, and Fertility	Data added on use of Janssen COVID-19 vaccine in pregnant women and data on use of other Janssen Ad26 based vaccines updated. Inclusion of number of breastfeeding women exposed to Janssen COVID-19 vaccine in Phase 3 clinical studies.
	Warnings and Precautions	Update to wording on TTS to provide more details on the population at risk of TTS as well as emphasise the need for immediate medical care.

Key: ADR=Adverse Drug Reaction; CCDS=Company Core Data Sheet; CLS= Capillary Leak Syndrome; COVID-19=Coronavirus Disease-2019; ITP= Immune Thrombocytopenia; TTS= Thrombosis with Thrombocytopenia Syndrome.

Please see Appendix 1.2 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 81,399 healthy participants have been enrolled in the Ad26.COV2.S clinical program, of which approximately 67,021 participants have received Ad26.COV2.S in the Company-sponsored interventional clinical trials (see Table 3). Of these, 580 participants were exposed to Ad26.COV2.S in the Phase 1 trials,[5] 935 participants were exposed to Ad26.COV2.S in a Phase 1/2a trial,[6] 1,554 participants were exposed to Ad26.COV2.S in the Phase 2 trials,[7] 537 participants were exposed to Ad26.COV2.S in the Phase 2a trial,[8] 109 participants were exposed to Ad26.COV2.S in the Phase 2/3 trial,[9] and over

[5] Trials included: VAC31518COV1002, and VAC31518COV1003.

[6] Trial included: VAC31518COV1001.

[7] Trials included: VAC31518COV2004, and VAC31518COV2008.

[8] Trial included: VAC31518COV2001.

[9] Trial included: VAC31518COV3006.

63,306 participants were exposed to Ad26.COV2.S in the Phase 3 trials.[10]

Additionally, 16,142 participants were exposed to Ad26.COV2.S in the pre-approval access programs,[11],and 751,589 participants were exposed to Ad26.COV2.S in the other studies.[12]

Table 3: Estimated Cumulative Subject Exposure from Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	67,021
Comparator	N/A
Placebo	39,056

Key: N/A=Not Applicable.
Number of participants exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date.
Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006 and VAC31518COV3009.
The number of participants exposed to study vaccine in blinded studies (VAC31518COV3005) are estimates.
A total of 24678 participants (506 participants from Trial VAC31518COV1001, 150 participants from Trial VAC31518COV2001, 15324 participants from Trial VAC31518COV3001, 530 participants from Trial VAC31518COV3005, 17 participants from Trial VAC31518COV3006, 8151 participants from Trial VAC31518COV3009) that received a regimen with both Ad26.COV2.S and placebo, participants are counted for both Ad26.COV2.S and placebo.

5.2. Cumulative and Interval Patient Exposure From Marketing Experience

Estimates of exposure are based on the number of delivered doses reported from LYNX Finance and administered doses reported from Centers for Disease Control and Prevention (CDC 2022) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2022) for European Economic Area (EEA) countries, Korea Disease Control and Prevention Agency (KDCA 2022) for South Korea, and Ministério da Saúde (Ministério da Saúde 2021) for Brazil.

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.

[10] Trials included: VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, and VAC31518COV3009.

[11] Programs included: VAC31518COV4006 and VAC31518COV4007.

[12] Studies included: COV-BOOST (VAC31518COV2009), VAC31518COV2012, VAC31518COV3012 (Sisonke [Together]), VAC31518COV3021 (Sisonke Boost Open-label Study), and DMID 21-0012.

Interval Exposure Estimates

The interval exposure for Ad26.COV2.S vaccine during the reporting period (01September 2021 to 28 February 2022)[13] is provided in Table 4.

Table 4: Subject Exposure to Ad26.COV2.S Vaccine During the Reporting Period (01 September 2021 to 28 February 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
EEA		
Austria	972,000	111,772
Belgium	0	75,303
Bulgaria	1,531,200	375,460
Croatia	165,600	135,116
Cyprus	96,000	10,251
Czechia	244,800	219,069
Denmark	504,000	0
Estonia	64,800	33,153
France	1,036,500	78,293
Germany	2,156,700	903,313
Greece	921,600	360,575
Hungary	3,388,800	195,797
Iceland	0	1,176
Ireland	0	7,720
Italy	0	66,628
Latvia	657,600	170,075
Liechtenstein	NR	261
Lithuania	144,000	127,572
Luxembourg	38,400	6,615
Malta	81,600	12,844
Netherlands	1,032,000	81,927
Norway	0	4,600
Poland	13,363,200	1,011,927
Portugal	415,200	55,878
Romania	2,999,000	1,470,203
Slovakia	295,200	120,243
Slovenia	110,400	53,606
Spain	0	55,982
ROW		
Afghanistan	3,232,800	NR
Algeria	5,680,800	NR
Angola	4,530,450	NR
Bangladesh	679,750	NR
Belize	16,800	NR
Benin	2,378,400	NR
Botswana	1,238,400	NR
Brazil	39,198,450	386,426
Burkina Faso	1,747,200	NR
Burundi	302,400	NR
Cameroon	940,800	NR
Canada	168,000	NR

[13] The data for the distributed/delivered doses in Lynx Finance is available for whole months only, therefore the exposure data was provided from 01 September 2021 to 28 February 2022, instead of the PBRER reporting period (25 August 2021 to 24 February 2022).

Table 4: Subject Exposure to Ad26.COV2.S Vaccine During the Reporting Period (01 September 2021 to 28 February 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Central African Republic	1,713,900	NR
Chad	811,100	NR
Colombia	11,020,000	NR
Congo (Brazzaville)	1,216,800	NR
Congo, (Kinshasa)	2,419,200	NR
Côte D'Ivoire	5,272,600	NR
Djibouti	50,400	NR
Egypt	15,251,850	NR
Ethiopia	25,266,000	NR
Gabon	866,400	NR
Gambia	52,800	NR
Ghana	8,611,200	NR
Guinea	907,200	NR
Guinea-Bissau	828,000	NR
Guyana	28,800	NR
Haiti	165,600	NR
Jamaica	100,800	NR
Kenya	10,115,450	NR
Lao PDR	763,200	NR
Lebanon	336,000	NR
Lesotho	622,650	NR
Liberia	885,600	NR
Madagascar	1,516,800	NR
Malawi	1,276,800	NR
Mali	393,600	NR
Mauritania	1,872,000	NR
Mauritius	331,200	NR
Mexico	1,350,000	NR
Mozambique	8,687,300	NR
Namibia	499,200	NR
Nepal	2,176,650	NR
Nicaragua	993,600	NR
Niger	2,606,400	NR
Nigeria	12,738,850	NR
Papua New Guinea	302,400	NR
Philippines	9,484,800	NR
Rwanda	897,600	NR
Saint Lucia	7,200	NR
Sao Tome And Principe	100,800	NR
Senegal	1,436,700	NR
Sierra Leone	1,048,800	NR
South Africa	15,996,000	NR
South Korea	2,818,600	271,274
South Sudan	901,750	NR
Sudan	3,292,000	NR
Switzerland	200	NR
Syrian Arab Republic (Syria)	3,458,400	NR
United Republic of Tanzania	522,700	NR
Togo	2,503,200	NR
Trinidad And Tobago	151,200	NR
Tunisia	1,432,800	NR
Turkey	832,800	NR
Uganda	12,036,000	NR

Table 4: Subject Exposure to Ad26.COV2.S Vaccine During the Reporting Period (01 September 2021 to 28 February 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Vanuatu	28,750	NR
Yemen	808,800	NR
Zambia	4,320,000	NR
US	**8,988,400**	**4,080,464**
Worldwide Total	***283,450,700***	***10,483,523***

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

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

b: Number of vaccine doses administered were reported from CDC for the US, from ECDC for EEA countries/territories, KDCA for South Korea, and from Ministério da Saúde for Brazil. Exposure data for administered doses for Brazil was only available from 01 September 2021 to 15 November 2021.

A total of 283,450,700 doses of Ad26.COV2.S vaccine were distributed worldwide from 01 September 2021 to 28 February 2022.

A total of 10,483,523 doses of Ad26.COV2.S vaccine were administered worldwide from 01 September 2021 to 28 February 2022.

Cumulative Exposure Estimates

The cumulative exposure for Ad26.COV2.S from launch to 28 February 2022 is provided in Table 5.

Table 5: Cumulative Exposure to Ad26.COV2.S Vaccine From Launch to 28 February 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
EEA		
Austria	1,292,400	362,624
Belgium	629,200	424,868
Bulgaria	1,777,300	507,924
Croatia	278,350	199,570
Cyprus	125,700	29,543
Czechia	492,000	411,018
Denmark	1,198,800	47,082
Estonia	110,800	77,707
Finland	68,400	NR
France	3,416,300	1,069,151
Germany	6,817,350	3,621,513
Greece	1,521,600	728,472
Hungary	3,939,600	331,501
Iceland[c]	33,500	54,283
Ireland	281,500	237,883
Italy	2,370,000	1,482,387
Latvia	767,800	275,799
Liechtenstein	NR	261
Lithuania[c]	236,800	294,274
Luxembourg	80,200	41,485
Malta	116,400	32,282
Netherlands	2,464,800	868,347

Table 5: Cumulative Exposure to Ad26.COV2.S Vaccine From Launch to 28 February 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Norway	403,900	7,012
Poland	15,523,300	2,754,984
Portugal[c]	993,600	1,132,827
Romania	4,080,300	2,036,849
Slovakia	475,200	182,706
Slovenia	230,400	136,523
Spain	2,659,000	1,980,541
Sweden	55,200	NR
ROW		
Afghanistan	6,544,850	NR
Algeria	6,285,600	NR
Angola	4,696,050	NR
Antigua and Barbuda	38,400	NR
Bahamas	38,400	NR
Bangladesh	679,750	NR
Belize	148,800	NR
Benin	2,680,800	NR
Bolivia	1,008,000	NR
Botswana	1,346,400	NR
Brazil	41,000,000	4,821,930
Burkina Faso	2,049,600	NR
Burundi	302,400	NR
Cambodia	1,060,100	NR
Cameroon	1,402,250	NR
Canada	168,000	NR
Central African Republic	2,016,300	NR
Chad	811,100	NR
Colombia	11,500,000	NR
Congo (Brazzaville)	1,519,200	NR
Congo, (Kinshasa)	2,419,200	NR
Côte D'ivoire	5,272,600	NR
Djibouti	201,600	NR
Egypt	15,513,450	NR
Ethiopia	26,942,150	NR
Gabon	866,400	NR
Gambia	355,200	NR
Ghana	8,788,800	NR
Guinea	907,200	NR
Guinea-Bissau	1,130,400	NR
Guyana	60,000	NR
Haiti	165,600	NR
Jamaica	216,000	NR
Kenya	10,417,850	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR
Lesotho	1,033,050	NR
Liberia	1,188,000	NR
Madagascar	1,819,550	NR
Malawi	1,581,150	NR
Mali	544,800	NR
Mauritania	2,282,400	NR
Mauritius	439,200	NR
Mexico	1,350,000	NR
Moldova	302,400	NR

Table 5: Cumulative Exposure to Ad26.COV2.S Vaccine From Launch to 28 February 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Morocco	302,400	NR
Mozambique	8,989,700	NR
Namibia	499,200	NR
Nepal	3,711,500	NR
Nicaragua	993,600	NR
Niger	2,908,800	NR
Nigeria	12,916,450	NR
Papua New Guinea	604,800	NR
Philippines	12,725,650	NR
Rwanda	897,600	NR
Saint Lucia	7,200	NR
Sao Tome and Principe	100,800	NR
Senegal	1,739,100	NR
Sierra Leone	1,101,600	NR
South Africa	19,623,200	NR
South Korea	2,919,400	1,515,259
South Sudan	901,750	NR
Sudan	3,898,700	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syrian Arab Republic (Syria)	3,458,400	NR
United Republic of Tanzania	1,581,150	NR
Togo	2,620,800	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	12,036,000	NR
Vanuatu	28,750	NR
Yemen	960,000	NR
Zambia	4,622,400	NR
US	**35,262,550**	**18,439,105**
Worldwide Total	***361,986,800[d]***	***44,105,710***

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; NR=Not Reported; PDR=People's Democratic Republic; ROW=Rest of World; US=United States.

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

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

c: 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.

d: The count also included the doses donated cumulatively by the US and EU to various countries/territories, including donations through the GAVI/COVAX agreement.

A total of 361,986,800 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 28 February 2022.

A total of 44,105,710 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 28 February 2022.

Homologous Ad26.COV2.S Booster Doses for Interval and Cumulative Periods

The list of countries/territories along with number of homologous Ad26.COV2.S booster doses for interval and cumulative periods is provided in Table 6.

Table 6: Total Number of Homologous Ad26.COV2.S Booster Doses

Country/Territory	Interval	Cumulative
South Korea	26,448	26,456
US[a]	1,427,984	1,427,984
Total	**1,454,432**	**1,454,440**

Key: US=United States.
a: Exposure data for booster doses for the US was available from 06 October 2021 onwards.

A total of 1,454,432 homologous Ad26.COV2.S booster doses were administered in South Korea and in the US from 01 September 2022 to 28 February 2022.

A total of 1,454,440 homologous Ad26.COV2.S booster doses were administered in South Korea and in the US from launch to 28 February 2022.

Exposure by Age for Ad26.COV2.S in EEA

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

Post-authorisation use in special populations

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

5.3. Other Post-approval Use

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

6. DATA IN SUMMARY TABULATIONS

Database

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

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

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

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

6.1. Reference Information

All events are coded using Medical Dictionary for Regulatory Activities (MedDRA), version 24.1. Caution is advised when comparing current data with those of PBRERs using earlier MedDRA versions/coding dictionaries.

6.2. Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials

Appendix 2.1.1 and Appendix 2.1.2 contain a cumulative tabulation of SAEs from Company-sponsored and non-Company-sponsored clinical trials, reported from the Developmental International Birth Date to the data lock date (DLD) of this 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 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 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

[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.

(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 one 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, 41,619 serious ARs and 87,403 nonserious ARs were received from spontaneous sources and 413 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 (43,975)
- Nervous System Disorders (19,815)
- Musculoskeletal and Connective Tissue Disorders (12,420)
- Infections and Infestations (9,261)
- Investigations (7,948)

Cumulatively, 69,597 serious ARs (69,082 spontaneous, 515 from non-interventional post-marketing studies and other solicited sources) were received by the Marketing Authorisation Holder (MAH).

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

Appendix 4.1 contains a list of MAH-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 ongoing during the reporting interval.

7.1. Completed Clinical Trials

A "completed clinical trial" is defined as a trial for which a final Clinical Study Report (CSR) is available (ie, CSR completed during the PBRER reporting period). There were no completed MAH-sponsored clinical trials during the reporting period.

[15] This does not include interventional clinical trials.

7.2. Ongoing Clinical Trials

An "ongoing clinical trial" is defined as a trial in which the first Informed Consent Form (ICF) has been signed, whether a hold is in place or analysis is complete, but for which a final CSR is not available at the data-lock point (DLP) for this PBRER, regardless of whether the last participant last visit has occurred.

A brief summary of all ongoing clinical trials (VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009) is presented below.

Trial VAC31518COV1001

This is a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged ≥18 to ≤55 years and aged ≥65 years in good health with or without stable underlying conditions to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2-dose levels, administered intramuscular (IM) as a single-dose or 2-dose schedule, with a single booster vaccination administered in 1 cohort.

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

Trial VAC31518COV1002

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

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

Trial VAC31518COV1003

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

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

Trial VAC31518COV2001

This is a Phase 2a, randomised, double-blind, placebo-controlled, multicentre trial evaluating Ad26.COV2.S at a range of dose levels and vaccination intervals in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive.

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

Trial VAC31518COV2004

This is a Phase 2, open-label 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.

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

Trial VAC31518COV2008

This is a Phase 2, randomised, double-blind, parallel, multicentre trial to evaluate the immunogenicity, reactogenicity, and safety of Ad26.COV2.S administered as a 1-dose booster vaccination regimen (5×10^{10} vp 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 (Cohort 1-homologous booster) or who previously received primary vaccination with the Pfizer BNT162b2 vaccine (Cohort 2 - heterologous booster).

Safety Summary

A summary of safety findings from the primary analysis of Trial VAC31518COV2008 with a cut-off date of 15 December 2021 is presented below:

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

For both the homologous and heterologous booster vaccinations, there was a decrease in the frequencies of solicited local AEs with the decreasing dose level. After the heterologous booster vaccination, there was a decrease in the frequency of overall solicited AEs, as well as solicited systemic AEs, as the dose level decreased, whereas such trend was not observed after the homologous booster vaccination.

Up to the cut-off date of 15 December 2021, no deaths were reported in the trial. Overall, SAEs were reported in 4 participants after the homologous booster vaccination (PTs: Myocardial infarction, Systemic inflammatory response syndrome and Chronic obstructive pulmonary disease, Multiple fractures, and Atrial fibrillation and Giant cell arteritis) and for 5 participants after the heterologous booster vaccination (PTs: Asthenia, Headache, Nausea, Fatigue, and Myalgia; Bipolar disorder, Pancreatitis, Suicidal ideation, and Asthma). There were no related SAEs reported after the homologous booster vaccination, whereas 1 participant was reported with a related SAEs after the heterologous booster vaccination.

A total of 6 AEs of thrombocytopenia were reported in 5 participants, with onset within 19 days after the homologous booster vaccination (Cohort 1). Of these 6 AEs of thrombocytopenia, 5 AEs were reported for participants that received a 2.5×1010 vp dose level and 1 event was reported in a participant that received the 5×1010 vp dose level (this event was considered to be a laboratory error). Two AEs of Grade 3 severity were considered related to the study vaccination. All the AEs of thrombocytopenia were resolved or resolving at the time of this report.

In conclusion, up to the cut-off date of 15 December 2021, the results from the descriptive safety and reactogenicity analyses show that the booster vaccination with Ad26.COV2.S at the 5×1010 vp, 2.5×1010 vp, and 1×1010 vp dose levels had an acceptable safety and reactogenicity profile with no safety issues identified. In general, a less reactogenicity was observed after the homologous booster vaccination than the heterologous booster vaccination. Also, a lower reactogenicity was observed in older adults (≥60 years of age) than in younger adults (≥18 to 59 years of age).

Trial VAC31518COV3001

This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy, and safety trial in adults ≥18 to <60 years of age and ≥60 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S will be evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. Additionally, the open-label phase of the trial is extended to include an open-label booster vaccination with a single dose of Ad26.COV2.S at the Year 1/Booster Visit. The combination of homologous or heterologous prime/boost vaccination is currently under evaluation.

Safety summary

A summary of safety findings from the final analysis of the double-blind phase of Trial VAC31518COV3001 with a cut-off date of 09 July 2021 is presented below:

The final analysis of the double-blind phase of Trial VAC31518COV3001 with a cut-off date of 09 July 2021, confirms the established safety profile of Ad26.COV2.S.

The single dose of Ad26.COV2.S at a dose level of 5×10^{10} vp has an acceptable safety and reactogenicity profile in adults ≥18 years of age, including adults ≥60 years of age. No significant safety issues were identified. In general, a lower reactogenicity was observed in older adults compared to younger adults in this analysis.

In the double-blind phase, 83 participants with 1 or more fatal AEs were reported: 28 in the Ad26.COV2.S group and 55 in the placebo group. During the entire trial, 100 participants with 1 or more fatal AEs were reported, of which 40 occurred in participants who received Ad26.COV2.S. Four deaths were reported after the open-label vaccination with Ad26.COV2.S. One of these events was considered related to the study vaccine by the investigator. This participant was reported to have a Grade 4 pulmonary embolism 57 days after the open-label vaccination with Ad26.COV2.S.

Of all participants receiving Ad26.COV2.S during the entire trial, 436 (1.2%) were reported with 1 or more SAE. In the double-blind phase, 223 (1.0%) participants were reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared to 265 (1.2%) participants in the placebo group. A total of 14 (0.1%) participants reported SAEs associated with COVID-19 in the Ad26.COV2.S group, compared to 100 (0.5%) participants in the placebo group.

During the entire trial, 19 participants were reported a total of 21 SAEs which were considered to be related to the study vaccine by the investigator: 19 events (reported in 18 participants) in the Ad26.COV2.S group (3 cases of ischemic stroke, 2 cases of Bell's Palsy, 2 cases of pulmonary embolism, 2 cases of deep vein thrombosis, Guillain-Barre syndrome (GBS), venous thrombosis limb, retinal vein thrombosis, atrial fibrillation, pericarditis, complex regional pain syndrome, post-vaccination syndrome, hypersensitivity, headache, and asthma) and 2 events (reported in 1 participant) in the placebo group (Epstein-Barr virus infection and atrial flutter).

One SAE of thromboembolic event with thrombocytopenia (venous transverse sinus thrombosis and cerebral hemorrhage) was reported following the administration of Ad26.COV2.S, and it was confirmed as a thrombosis with thrombocytopenia syndrome (TTS) meeting both the Level 1 criteria using the Brighton Collaboration (BC) level of certainty and the Center for Disease Control and Prevention definition for a tier 1 TTS case and could therefore be confirmed as a TTS according to both case definitions.

The following AEs of interest had a numerical imbalance between the Ad26.COV2.S and placebo group: tinnitus, seizures, and embolic and thrombotic events. Tinnitus was considered an adverse reaction. Further review of events of seizure and embolic and thrombotic events revealed that the majority had predisposing, underlying medical conditions, and these were not considered safety concerns upon the further evaluation; the number of events contributing to the imbalance was small, and these imbalances were not observed in Trial VAC31518COV3009. A limited number of medically attended adverse events (MAAEs) of at least Grade 3, none of which were considered as a safety issue, and no events of anaphylaxis were reported in the Ad26.COV2.S group in Trial VAC31518COV3001.

Finally, the lack of efficacy against COVID-19 could constitute a safety concern. The totality of a data available at present time 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. Further details are provided in Section 13.

Overall, no new safety concerns have been identified after an Ad26.COV2.S primary dose.

Trial VAC31518COV3003

This is a Phase 3, randomised, double-blind trial to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults aged 18 to 55 years, inclusive. This trial consists of 2 parts: main trial and sub trial. In the main trial, the safety, reactogenicity, and immunogenicity of 1 dose (dose 1 of the 2-dose regimen) and 2 doses of Ad26.COV2.S will be evaluated. In the sub trial, additional adult participants aged 18 to 55 years will be enrolled (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 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 2/3, randomised, observer-blind, pivotal adaptive trial to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a 1- or 2-dose regimen in healthy adolescents aged 12 to 17 years inclusive.

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

Trial VAC31518COV3009

This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S is being evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine. Additionally, participants from the placebo arm enrolled during the double-blind phase have been offered to receive a single dose of Ad26.COV2.S (open-label vaccination), unless they met certain vaccination discontinuation rules during the double-blind phase of the trial. At present time, the open-label phase of the trial is extended to include an open-label booster vaccination with a single dose of Ad26.COV2.S to all participants that have received only single dose of Ad26COV2.S in the trial.

Safety summary

A summary of safety findings from the final analysis of the double-blind phase of Trial VAC31518COV3009 with a cut-off date of 25 June 2021 is presented below:

The final analysis of the double-blind phase of Trial VAC31518COV3009 with a cut-off date of 25 June 2021, confirms the established safety profile of Ad26.COV2.S.

The 2-dose schedule of Ad26.COV2.S at a dose level of 5×10^{10} vp has an acceptable safety and reactogenicity profile in adults ≥18 years of age, including adults ≥60 years of age. No significant safety issues were identified. In general, a lower reactogenicity was observed in older adults

compared to younger adults in this analysis.

Up to the cutoff date of 25 June 2021, 17 deaths were reported during the double-blind phase: 4 in the Ad26.COV2.S group and 13 in the placebo group.

SAEs were reported for 240 participants (104 [0.7%] participants in the Ad26.COV2.S group and 136 [0.9%] participants in the placebo group). No increase in the frequency of SAEs was observed post-booster compared with the post-dose 1. A total of 98 (0.6%) participants reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared with 104 (0.7%) participants in the placebo group. A total of 8 (0.1%) participants reported SAEs associated with COVID-19 in the Ad26.COV2.S group compared with 36 (0.2%) participants in the placebo group.

Related SAEs were reported in 8 participants in the Ad26.COV2.S group and 3 participants in the placebo group. In the Ad26.COV2.S group after the first dose, the related SAEs were pyrexia, pericarditis, allergy to vaccine, and hemoptysis in 1 participant each, and injection site swelling vertigo, and myocardial necrosis marker increased in 1 participant. Related SAEs after the booster dose were facial paresis, pulmonary embolism, and cerebrovascular accident in 1 participant each.

Numerical imbalances that were observed in Trial VAC31518COV3001 for the AEs of interest pulmonary embolism, deep vein thrombosis, and convulsions/seizures were not observed in Trial VAC31518COV3009. A numerical imbalance between the Ad26.COV2.S group and the placebo group for hemorrhagic disorders was observed in Trial VAC31518COV3009 (55 versus 29 in the double-blind phase), but this was not observed in Trial VAC31518COV3001 (48 versus 77 in the double-blind phase). In Trial VAC31518COV3009, numerical imbalances were also observed for arthritis (38 versus 22) and tinnitus (9 versus 5). An imbalance for arthritis was not observed in the double-blind phase of Trial VAC31518COV3001 (40 versus 42). In Trial VAC31518COV3009, the imbalance for arthritis between the Ad26.COV2.S group and the placebo group was observed in the 28-day period post-dose 1 (24 versus 12) but not post-booster (4 versus 5). Similarly for tinnitus, the imbalance in Trial VAC31518COV3009 was observed in the 28-day period post-dose 1 (4 versus 2) but not post-booster (2 versus 2).

A limited number of MAAEs of at least Grade 3, none of which were considered as a safety issue, and no events of anaphylaxis were reported in the Ad26.COV2.S group in Trial VAC31518COV3009.

Overall, no new safety concerns have been identified after an Ad26.COV2.S primary or booster dose.

Independent Data Monitoring Committee/Data Safety Monitoring Board

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

7.3. Long-term Follow-up

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

7.4. Other Therapeutic Use of Medicinal Product

During this reporting period, 1 pre-approval access program (VAC31518COV4007) of Ad26.COV2.S was completed and no other program of Ad26.COV2.S was ongoing. No clinically important safety information from the completed program (VAC31518COV4007) that follow a specific protocol (solicited reporting as per International Council on Harmonisation [ICH] E2D) was identified during the reporting period.

7.5. New Safety Data Related to Fixed Combination Therapies

This section is not applicable as there are no marketed combination therapies with Ad26.COV2.S.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Based on review of the data from non-interventional study for Ad26.COV2.S during the reporting period, no new information with potential impact to the benefit-risk assessment has been identified (see Appendix 4.2).

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

During the PBRER reporting period, 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by University Hospital Southampton National Health Service (NHS) Foundation Trust, 1 interventional clinical study (VAC31518COV2012) sponsored by Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand), 2 interventional clinical studies (VAC31518COV3012 [Sisonke {Together}] and VAC31518COV3021 [Sisonke Boost Open-Label Study]) sponsored by South African Medical Research Council (SAMRC), and 1 interventional clinical study (Division of Microbiology and Infectious Diseases [DMID] 21-0012) sponsored by National Institutes of Health (NIH) were ongoing for Ad26.COV2.S. Of these 5 studies, 2 studies (VAC31518COV2012 and VAC31518COV3021) were initiated during the PBRER reporting period. The summary and safety findings from these studies are presented below:

Study COV-BOOST (VAC31518COV2009)

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

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

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

Study VAC31518COV2012

This is Phase 1/2, prospective, multi-centre, observer-blind adaptive study to assess the safety, reactogenicity, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 years of age in Study Part A and Part B. A total of 550 participants will be recruited. If the optional Group (A4) is feasible and enrolled, the total recruitment will be 610 participants. Priority enrolment is given to Groups A1 and A2, followed by Groups A4 and B1. Enrolment of groups are open-label allocation and assessor-masked.

At the time of DLD of this PBRER, 468 participants received Ad26.COV2.S in this study.

During the PBRER reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available other than those presented in the RSI.

Study VAC31518COV3012 (Sisonke [Together])

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

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

During the PBRER reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available other than those presented in the RSI.

Study VAC31518COV3021 (Sisonke Boost Open-label Study)

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

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

During the PBRER reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available other than those presented in the Reference Safety Information (RSI).

Study DMID 21-0012

This is a Phase 1/2, open-label study in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This study is designed to assess the safety, reactogenicity, and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of Emergency Use Authorisation dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).

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

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

9.2. Medication Errors

Introduction

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

Methods

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

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 1,655 (893 medically confirmed and 762 medically unconfirmed) cases reporting medication errors were identified. Of these cases, 104 were serious and 1,551 nonserious, and reported a total of 1,882 events (27 serious; 1,855 nonserious).

[16] Of note, the use of the SMQ Medication Errors (broad) includes PTs, such as Product use in unapproved indication and Drug administered to patient of inappropriate age, that could be used to describe off label use. However, these terms could also involve accidental use and are, therefore, included for completeness. It should be noted that the PT Off label use is not included in the SMQ Medication Errors (broad) since off label use may be considered as intentional; as these cases are usually not analysed in this section; however, for transparency reasons the cases containing this term are included in this section.

Of these 1,655 cases during the reporting period of 25 August 2021 to 24 February 2022, 2 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 1,652 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 3,070 (1,828 medically confirmed and 1,242 medically unconfirmed) cases reporting medication errors were identified. Of these cases, 219 were serious and 2,851 nonserious, and reported a total of 3,731 events (48 serious; 3,683 nonserious).

Of these 3,070 cumulative cases received, 6 were reported from Janssen Sponsored Clinical Studies, 24 from Janssen Supported Clinical Studies, and 3,042 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 7 below.

Table 7: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Period=1,655	Number of Cases Received Cumulatively=3,070
Sex	Male	753	1,204
	Female	600	1,079
	NR	302	787
Age (Years)[a] **Minimum: 0.67** **Maximum: 98** **Mean: 44** **Median: 42**	<18	93	357
	18 to 35	306	441
	36 to 50	317	456
	51 to 64	253	435
	≥65	168	275
	Adolescent	5	14
	Child	1	4
	Adult	21	45
	Elderly	3	6
	NR	488	1,037
Source	Spontaneous	1,371	2,757
	Clinical study (non-interventional; solicited)	280	281
	Clinical study (interventional; non-solicited)	2	6
	Clinical Study (non-interventional; non-solicited)	2	26
Country/Territory[b,c]	United States	1,201	2,239
	Brazil	193	227
	Germany	40	60
	Canada	25	25
	Greece	24	27
	Korea, Republic of	21	25
	France	18	84
	Colombia	15	62

Table 7: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Period=1,655	Number of Cases Received Cumulatively=3,070
	South Africa	12	13
	Romania	11	12
	Hungary	10	12
	Austria	8	11
	Portugal	8	17
	Italy	7	13
	Bulgaria	6	7
	Netherlands	6	11
	Latvia	5	102
	Spain	5	12
	Ireland	4	12
	Mexico	4	6
	New Zealand	4	4
	Poland	4	21
	Belgium	3	30
Event Characteristics		**Number of Events=1,882**	**Number of Events=3,731**
Seriousness (Event Level)[c]	Nonserious	1,855	3,683
	Serious	27	48
Outcome (Event Level)[c]	Resolved	16	54
	Not resolved	13	39
	Fatal	2	3
	NR	1,851	3,630

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥3 have been presented by decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting medication errors with the use of Ad26.COV2.S is presented in Table 8 below. A single case may contain more than 1 event(s) of interest (EOI).

Table 8: Frequency Distribution of MedDRA PTs of Interest in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Inappropriate schedule of product administration	0	611	1	650
Expired product administered	2	396	4	531
Poor quality product administered	0	230	0	597

Table 8: Frequency Distribution of MedDRA PTs of Interest in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product storage error	0	168	2	472
Product administered to patient of inappropriate age	1	98	3	357
Underdose	0	87	1	185
Medication error	2	56	2	157
Overdose	3	40	7	61
Incorrect dose administered	0	39	2	122
Incorrect route of product administration	0	29	3	144
Extra dose administered	0	17	0	54
Product use in unapproved indication	0	16	0	18
Interchange of vaccine products	6	8	6	11
Vaccination error	2	10	2	17
Wrong technique in product usage process	0	11	0	29
Product temperature excursion issue	0	10	0	40
Product lot number issue	0	6	0	6
Wrong product administered	0	6	0	24
Product administration error	2	3	2	65
Product administered at inappropriate site	1	2	1	15
Accidental exposure to product	2	0	2	17
Drug delivery system malfunction	0	2	0	3
Product barcode issue	0	2	0	3
Product use issue	0	2	1	34
Syringe issue	0	2	0	16

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

a: MedDRA PTs with frequency ≥2 have been presented by decreasing order for the current reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Of the 1,655 cases retrieved during the reporting period, 882 reported the PT of Off Label Use, 99 reported Product administered to patient of inappropriate age, 29 reported Incorrect route of product administration, and 16 reported Product use in unapproved indications.

Medication Errors With Harm

A frequency distribution of additional relevant AEs (n≥10) involving the use of Ad26.COV2.S in cases is provided in Table 9.

Table 9: Frequency Distribution of Additional Relevant AEs (n≥10) in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	3	134	10	231
Headache	4	122	11	229
Myalgia	2	100	5	129
Fatigue	2	98	9	164
Chills	2	77	4	141
Pain	1	71	6	129
Injection site pain	1	61	2	107
Pain in extremity	4	48	10	126
Chest pain	6	44	8	52
Nausea	4	43	6	85
Diarrhoea	3	43	6	55
Dizziness	1	43	5	69
Arthralgia	1	40	3	62
Dyspnoea	5	36	10	49
Malaise	2	28	5	45
Vomiting	5	19	5	33
Asthenia	3	19	4	37
Vaccination site pain	0	22	0	24
Feeling abnormal	0	21	2	39
Heart rate increased	1	20	2	23
Paraesthesia	1	19	2	35
Insomnia	2	13	4	31
Back pain	0	14	2	23
Pruritus	0	14	0	15
Cough	3	10	4	19
Injection site erythema	0	13	0	16
Lymphadenopathy	0	13	0	14
Hypoaesthesia	1	11	3	23
Oropharyngeal pain	0	11	1	18
Tinnitus	1	10	2	18
Contusion	0	10	1	19
Hyperhidrosis	3	7	4	22
Tremor	1	9	1	17

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

a: A single case may report more than 1 MedDRA PT. MedDRA PTs with frequency ≥10 have been presented.

b: The MedDRA PTs of interest were sorted by descending frequency for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 2 cases reporting medication error were retrieved from Janssen Sponsored Clinical Studies. Both cases were from VAC31518COV3001 and reported serious EOI of accidental overdose and overdose. It was reported that these cases concerned overdose with opiates and seroquel and not with Ad26.COV2.S. No medication error cases associated with the use of Ad26.COV2.S were identified from Janssen Sponsored Clinical Studies.

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting a medication error was retrieved from Janssen Sponsored Clinical Studies. This case was from VAC31518COV4007 and concerned a 39-year-old female from [redacted]. This case reported the nonserious PT of Medication error with no additional AEs reported.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 1,652 cases reporting medication errors were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 1,652 cases reported 25 serious EOI. Of these 1,652 cases, the most frequently reported country/territory of origin was the US (n=1,199) followed by Brazil (n=192), and Germany (n=40). Of the 1,652 cases, 752 cases concerned males, 598 females, and 302 had no sex reported. The age range was 0.67 to 98 years.

A frequency distribution of 1,879 MedDRA PTs of interest involving the use of Ad26.COV2.S in 1,652 cases is provided in Table 10.

Table 10: Frequency Distribution of MedDRA PTs of Interest in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Received During the Reporting Period[a]	
	Serious	Nonserious
Inappropriate schedule of product administration	0	611
Expired product administered	2	396
Poor quality product administered	0	230
Product storage error	0	168
Product administered to patient of inappropriate age	1	98
Underdose	0	87
Medication error	2	55
Overdose	2	40
Incorrect dose administered	0	39
Incorrect route of product	0	29

Table 10: Frequency Distribution of MedDRA PTs of Interest in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Received During the Reporting Period[a]	
	Serious	Nonserious
administration		
Extra dose administered	0	17
Product use in unapproved indication	0	16
Interchange of vaccine products	6	8
Vaccination error	2	10
Wrong technique in product usage process	0	11
Product temperature excursion issue	0	10
Product lot number issue	0	6
Wrong product administered	0	6
Product administration error	2	3
Product administered at inappropriate site	1	2
Accidental exposure to product	2	0
Drug delivery system malfunction	0	2
Product barcode issue	0	2
Syringe issue	0	2

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: MedDRA PTs with frequency ≥2 have been presented. A single case may report more than 1 MedDRA PT of interest.

Two EOI had a fatal outcome, 1 of which referred to another medication (overdose of wellbutrin), and 1 concerned a 48-year-old male who experienced cerebral vein sinus thrombosis (CVST) and died of an unknown cause 13 days post-vaccination. Approximately, 5.6 months prior to receiving Ad26.COV2.S, the patient received 2 doses of BNT 162 (PT: Interchange of vaccine products).

The majority of the cases involved medication errors without harm. No AEs were reported in 1,030 of the 1,652 cases with medication error.

Medication Error With Harm in Post-marketing Sources (Including Spontaneous and Solicited Cases)

A frequency distribution of AEs (n≥10) involving the use of Ad26.COV2.S in the remaining 622 cases is provided in Table 11. Of the 622 cases, 96 were serious and 526 were nonserious. The most frequently reported events represented local or systemic reactogenicity to Ad26.COV2.S.

Table 11: Frequency Distribution of Additional Relevant AEs (n≥10) in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

Additional AEs	Number of Events Received During the Reporting Period[a]	
	Serious	Nonserious
Pyrexia	3	134
Headache	4	122
Myalgia	2	100
Fatigue	2	98
Chills	2	77
Pain	1	71
Injection site pain	1	61
Pain in extremity	4	48
Chest pain	6	44
Nausea	4	43
Diarrhoea	3	43
Dizziness	1	43
Arthralgia	1	40
Dyspnoea	5	36
Malaise	2	28
Vomiting	5	19
Asthenia	3	19
Vaccination site pain	0	22
Feeling abnormal	0	21
Heart rate increased	1	20
Paraesthesia	1	19
Insomnia	2	13
Back pain	0	14
Pruritus	0	14
Cough	3	10
Injection site erythema	0	13
Lymphadenopathy	0	13
Hypoaesthesia	1	11
Oropharyngeal pain	0	11
Tinnitus	1	10
Contusion	0	10
Hyperhidrosis	3	7
Tremor	1	9

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

a: MedDRA PTs with frequency ≥10 have been presented. A single case may report more than 1 MedDRA PT

Paediatric Cases

During the reporting period of 25 August 2021 to 24 February 2022, 99 (60 medically confirmed and 39 medically unconfirmed) cases reporting medication errors were identified in the paediatric population. Of these cases, 20 were serious and 79 nonserious, and reported a total of 108 events (4 serious; 104 nonserious).

All of these 99 cases received during the reporting period of 25 August 2021 to 24 February 2022 were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 375 (188 medically confirmed and 187 medically unconfirmed) cases reporting medication errors in the paediatric population were identified. Of these cases, 29 cases were serious and 346 nonserious, and reported a total of 403 events (6 serious; 397 nonserious).

All of these 375 cumulative cases received were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

An overview of these cases is presented in Table 12 below.

Table 12: Characteristics of Paediatric Cases Involving the Use ofAd26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Period=99	Number of Cases Received Cumulatively=375
Sex	Male	43	187
	Female	37	133
	NR	19	55
Age (Years)[a]	<12	5	5
Minimum: 0.667	12 to 17	88	352
Maximum: 17	Adolescent	5	14
Mean: 15	Child	1	4
Median: 16			
Sources	Spontaneous	98	373
	Clinical study (non-interventional; solicited)	1	2
Country/Territory[b]	United States	62	175
	Latvia	5	102
	Portugal	5	6
	Romania	5	6
	Germany	4	6
	Bulgaria	2	3
	Austria	2	4
	Greece	2	2
	Italy	2	2
Event Characteristics		**Number of Events=108**	**Number of Events=403**
Seriousness (Event Level)[c]	Nonserious	104	397
	Serious	4	6

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥2 have been presented by decreasing order for the current reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 event of interest.

The frequency distribution of the MedDRA PTs of interest in paediatric cases reporting medication errors with the use of Ad26.COV2.S is presented in Table 13 below. A single case may contain more than 1 EOI.

Table 13: Frequency Distribution of MedDRA PTs of Interest in Paediatric Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age	1	91	3	346
ME	1	3	1	4
Vaccination error	0	3	0	3
Expired product administered	0	2	0	2
Accidental exposure to product	2	0	2	1
Poor quality product administered	0	2	0	4
Underdose	0	1	0	10
Wrong product administered	0	1	0	4
Incorrect route of product administration	0	1	0	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: MedDRA PTs have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 event of interest.

Medication Errors With Harm in Paediatric Cases

The frequency distribution of the additional AEs in paediatric cases reporting medication errors with the use of Ad26.COV2.S is presented in Table 14 below. A single case may contain more than 1 EOI.

Table 14: Frequency Distribution of Additional Relevant AEs (n≥2) in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

Additional AEs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	0	9	0	41
Pyrexia	1	6	2	42
Pain in extremity	0	3	0	26
Myalgia	1	2	1	5
Injection site pain	0	3	0	6
Malaise	0	3	1	9
Cardiac disorder	1	1	1	1
Presyncope	0	2	0	2
Pain	0	2	1	5
Fatigue	0	2	0	11

Table 14: Frequency Distribution of Additional Relevant AEs (n≥2) in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors

Additional AEs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Syncope	2	0	2	0
Guillain-Barre syndrome	2	0	2	0
Tremor	0	2	0	2

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

a: A single case may report more than 1 MedDRA PT. MedDRA PTs with frequency ≥2 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 event of interest.

Janssen Sponsored Clinical Studies

There were no paediatric cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no paediatric cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 99 cases reporting medication errors were retrieved in the paediatric population from Post-marketing sources (including spontaneous and solicited cases). These 99 cases reported 108 EOI (4 serious; 104 nonserious). Of these 99 cases, the most frequently reported country/territory of origin was the US (n=62) followed by Latvia, Portugal, and Romania (n=5 each). Of the 99 cases, 43 concerned males, 37 females, and 19 had no sex reported. The age range was 0.667 to 17 years.

The EOI (≥3) included product administered to patient of inappropriate age (n=92), medication error (n=4), and vaccination error (n=3).

No AEs were reported in the majority of the cases (n=65). The most frequently reported AEs (n≥7) involving the use of Ad26.COV2.S in the remaining 34 cases from post-marketing sources were headache (n=9), and pyrexia (n=7). There were no safety concerns identified from the review of these paediatric cases.

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the known information about medication errors.

No trend was identified in medication errors arising from the use of multi-dose vials as there were a limited number of overdose cases received with 2 during this PBRER reporting period and 40 cumulatively.

Fatal Cases

There were 14 cases with a fatal outcome including 5 paediatric cases, with none reporting a fatal EOI. All 5 cases were medically unconfirmed. The cause of death was not specified in 4 of the cases. The 4 cases concerned a 13-year-old male who had severe pre-existing heart and vascular conditions; a 4-year-old with an unspecified adverse reaction; a 13-year old male who experienced "blood clot and inflammation around heart"; and a "baby boy" without further information. The cause of death in the fifth case concerned to a 15-year-old male was streptococcal pharyngitis.

Of the remaining 9 cases, 5 involved adults and 1 an elderly patient. In 3 of the 9 cases, the patient's age was not specified. Cause of death, where reported included Intracranial aneurysm (n=1), Haemorrhagic stroke (n=1), Overdose (of wellbutrin; n=1) and Suspected COVID-19, Cardiac failure acute, Small cell lung cancer (n=1). In 5 of the 9 cases, the cause of death was not specified.

Booster Dose

Cumulatively, 727 (192 medically confirmed and 535 medically unconfirmed) cases were identified reporting medication errors in individuals who received the booster dose. Of these 727 cases, 453 had additional AEs. There were 40 serious and 687 nonserious cases. Of these cases, 573 were homologous and 154 were heterologous. Council for International Organisation of Medical Sciences (CIOMS II) Line Listing (LL) is presented in Appendix 7.1.

Conclusion

No new safety issues were identified through review of cases with medication errors, including paediatric cases. Overall, no new patterns of cases reporting medication errors or potential medication errors were identified. In addition, no relevant information on patterns of medication errors or potential medication errors has been identified for Ad26.COV2.S from other sources.

10. NON-CLINICAL DATA

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

11. LITERATURE

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

The MAH 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 program 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 MAH becomes aware of new safety/efficacy information from unpublished abstracts/manuscripts these would also be considered for evaluation and the findings will be discussed.

Selected references and Sponsor Comments are presented below.

11.1. Product-Specific Literature

Yadav R, Shah S, Chhetri S. ANCA-Associated Vasculitis Following Johnson and Johnson COVID-19 Vaccine. (Published online 2021).

Abstract: Antineutrophil cytoplasmic autoantibodies associated vasculitis (AAV) is characterised by antibodies against antigens in cytoplasmic granules of neutrophils and predominantly affects small vessels. AAV after COVID-19 messenger ribonucleic acid (mRNA) vaccination has been reported. We report rare case of AAV in a patient who presented with rapidly progressive glomerulonephritis (RPGN) after Johnson & Johnson vaccine administration.

MAH Comments: This case report of a 52-year-old female was presented in the 01 November 2021 to 15 January 2022 SSR (see Adverse Event Report Number [AER]# [redacted]) who presented with fever, joint pain, weakness, leukocytosis with left shift (21,000/mm3 with 92% polymorphonuclear cells), and dual positivity for p-ANCA and c-ANCA. The differential for the patient's presentation is extensive (Falk 2022), and infectious etiologies, including bacteremia and infective endocarditis, may present with a dual positive c-ANCA and p-ANCA (Veerappan 2012) as in this case. No information on blood cultures was provided, and echocardiographic findings (unspecified if transesophageal or transthoracic) did not include pertinent positives or negatives regarding valvular morphology (e.g., presence/absence of vegetations). Taking into consideration multiple potential etiologic factors, treatment with antibiotics, and missing information in this case (including outcome), no new safety information is detected at this time. See Section 16.2.1.1.1., Vasculitis for additional data during this time period.

Lee KA, Kim YJ, Jin HY. Thyrotoxicosis after COVID-19 vaccination: seven case reports and a literature review. Endocrine. 2021:74(3):470–472

No abstract available.

MAH Comments: The article describes "*seven independent patients who visited Jeonbuk National University Hospital from March 2021 to July 2021, all presenting with thyrotoxicosis after*

COVID-19 vaccination. The underlying etiologies were identified through diagnostic workup, with three cases of Graves' disease (GD), two cases of subacute painful thyroiditis (SAT), one case of concurrent GD and SAT, and one case of painless thyroiditis (PT)."

Three ([redacted]) out of 7 cases were reported after the Janssen vaccine: males between the ages of 34 to 39 years diagnosed with recurrent GD (n=1), concurrent Graves' and subacute thyroiditis (n=1), and painless thyroiditis with thyrotoxic periodic paralysis (n=1). Two patients "*did not undergo thyroid function test before vaccination although had no symptoms*" and 1 patient had a "*normal thyroid function performed at our hospital before vaccinations*" at an unspecified point in time. No information on other medical history, medications, treatment, or outcome were provided. Based on the limited clinical information available on each subject, no new safety signal has been identified.

Lipkind, H., Vazquez-Benitez, G., DeSilva, M., Vesco, K., Ackerman-Banks, C., Zhu, J., Boyce, T., Daley, M., Fuller, C., Getahun, D., Irving, S., Jackson, L., Williams, J., Zerbo, O., McNeil, M., Olson, C., Weintraub, E. and Kharbanda, E., 2022. Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth-Eight Integrated Health Care Organizations, United States, December 15, 2020–July 22, 2021. MMWR. Morbidity and Mortality Weekly Report, 71(1), pp.26-30.

Abstract (Summary): "*What is already known about this topic? Pregnant women with COVID-19 are at increased risk for severe illness and adverse birth outcomes, yet many remain reluctant to be vaccinated. What is added by this report? In a retrospective cohort of >40,000 pregnant women, COVID-19 vaccination during pregnancy was not associated with preterm birth or small-for-gestational-age at birth overall, stratified by trimester of vaccination, or number of vaccine doses received during pregnancy, compared with unvaccinated pregnant women. What are the implications for public health practice? These data support the safety of COVID-19 vaccination during pregnancy.*"

MAH Comments: Of the 10,064 singleton pregnancies with information on gestational age, an outcome of live birth, and otherwise meeting the authors' inclusion and exclusion criteria, 424 received the Janssen vaccine; last administration of any vaccine was in July 2021 (pre-booster), and no further breakdown on outcomes was provided. Regarding trimester of administration, the authors note that "*Because of the small number of first-trimester exposures, aHRs [adjusted hazard ratios for pre-term birth or small for gestational age] for first-trimester vaccination could not be calculated.*" The Pregnancy, Breastfeeding and Fertility Section of the CCDS states: "*Safety data with TRADENAME when administered within 3 months before pregnancy as well as during pregnancy have shown no safety concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes*". No new safety information is detected at this time. See Section 16.3.5.1., Use in Pregnancy for additional data for this time period.

Kinariwalla, N., London, A., Soliman, Y., Niedt, G., Husain, S. and Gallitano, S., 2022. A case of generalized Sweet syndrome with vasculitis triggered by recent COVID-19 vaccination. JAAD Case Reports, 19, pp.64-67.

No abstract available; a summary by the MAH is as follows:

The authors present a "*54-year-old male with no significant past medical history presented to the emergency department in significant pain, with tongue swelling and ulceration. The patient denied fevers, chills, night sweats and weight loss. He received the Janssen Ad26.COV2.S vaccine nine days prior to onset of symptoms.*"

"*On physical examination, he had an erythematous, fissured tongue with confluent erosions and dozens of firm, blanching and erythematous and papulonecrotic nodules on the extremities and trunk). The scrotum had flesh colored and erythematous plaques. The plantar feet had erythematous and targetoid macules. The patient's lesions progressed over one week, and he developed new eroded and crusted plaques on the scalp, trunk, and extremities. The genital (Figure 1D) and plantar foot lesions became more targetoid in appearance*."

"*Lab work revealed a leukocytosis to 10.84x103/uL with 90% neutrophils and erythrocyte sedimentation rate (ESR) of 29 mL/hour and C-reactive protein (CRP) of 19.6 mg/L. Serum protein electrophoresis (SPEP) resulted in a positive abnormal monoclonal IgA lambda*."

The skin biopsy for H&E revealed *"a dense interstitial and perivascular neutrophilic infiltrate with leukocytoclasia and focal fibrin deposition in blood vessel walls (Figure 2A-C). [...] The patient was treated with a ten-day course of steroids with significant improvement of lesions. Furthermore, repeat SPEP approximately 10 weeks after disease onset showed resolution of monoclonal IgA lambda*."

According to the authors, "*we diagnosed a case of SS with vasculitis and transient monoclonal IgA gammopathy, triggered by the Janssen Ad26.COV2.S vaccine." They stated, "Following treatment, the IgA monoclonal gammopathy resolved, highlighting the transient nature of immunoglobulin response and subsequent vasculitis*."

MAH Comments: Sweet Syndrome has been associated with a broad range of conditions including hematologic malignancies (Merola 2020). In the present case, the authors report an "*abnormal monoclonal IgA lambda*" for which a bone marrow biopsy was not performed. Given the background frequency of monoclonal gammopathies in this demographic (Laubach 2022) and an absence of clinical work up, no new safety information is detected at this time (see AER# [redacted]).

11.2. Class Effect Literature

Karrow NA, Shandilya UK, Pelech S, et al. Maternal COVID-19 Vaccination and Its Potential Impact on Fetal and Neonatal Development. *Vaccines*. 2021;9(11):1351.

Abstract: Vaccines have been developed at "*warp speed*" to combat the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus. Although they are considered the best approach for preventing mortality, when assessing the safety of these vaccines, pregnant women have not been included in clinical trials. Thus, vaccine safety for this demographic, as well as for the developing fetus and neonate, remains to be determined. A global effort has been underway to encourage pregnant women to get vaccinated despite the uncertain risk posed to them and their offspring. Given this, post-hoc data collection, potentially for years, will be required to determine the outcomes of COVID-19 and vaccination on the next generation. Most COVID-19 vaccine reactions include injection site erythema, pain, swelling, fatigue, headache, fever and lymphadenopathy, which may be sufficient to affect fetal/neonatal development. In this review, we have explored components of the first-generation viral vector and mRNA COVID-19 vaccines that are believed to contribute to adverse reactions, and which may negatively impact fetal and neonatal development. We have followed this with a discussion of the potential for using an ovine model to explore the long-term outcomes of COVID-19 vaccination during the prenatal and neonatal periods.

MAH Comments: The authors state "*In closing, we currently have no data to assess the outcome of maternal COVID-19 vaccination on offspring health, and this may take years to generate*." Use during pregnancy is classified as Missing Information in the Core Risk Management Plan (cRMP) for

COVID-19 Vaccine Janssen; both a pregnancy registry (VAC31518COV4005) and an open-label phase 2 study in pregnant patients (VAC31518COV2004) are included in the Pharmacovigilance Plan. The Pregnancy, Breastfeeding and Fertility Section of the CCDS states: "*Administration of TRADENAME in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and fetus (see Warnings and Precautions).*" No new safety information is detected at this time.

Westrop SJ, Whitaker HJ, Powell AA, et al. Real-world data on immune responses following heterologous prime-boost COVID-19 vaccination schedule with Pfizer and AstraZeneca vaccines in England. Journal Infection. Published online 04 February 2022.

Abstract: There are limited data on immune responses to heterologous COVID-19 immunisation schedules, especially following an extended ≥12-week interval between doses.

Methods: SARS-CoV-2 infection-naïve and previously-infected adults receiving ChAd-BNT (ChAdOx1 nCoV-19, AstraZeneca followed by BNT162b2, Pfizer-BioNTech) or BNT-ChAd as part of the UK national immunisation programme provided blood samples at 30 days and 12 weeks after their second dose. Geometric mean concentrations (GMC) of anti-SARS-CoV-2 spike (S-antibody) and nucleoprotein (N-antibody) IgG antibodies and geometric mean ratios (GMR) were compared with a contemporaneous cohort receiving homologous ChAd-ChAd or BNT-BNT.

Results: During March-October 2021, 75,827 individuals were identified as having received heterologous vaccination, 9,489 invited to participate, 1,836 responded (19.3%) and 656 were eligible. In previously-uninfected adults, S-antibody GMC at 30 days post-second dose were lowest for ChAd-ChAd (862 [95% CI, 694 – 1069]) and significantly higher for ChAd-BNT (6233 [5522-7035]; GMR 6.29; [5.04–7.85]; p<0.001), BNT-ChAd (4776 [4066–5610]; GMR 4.55 [3.56–5.81]; p<0.001) and BNT-BNT (5377 [4596–6289]; GMR 5.66 [4.49–7.15]; p<0.001). By 12 weeks after dose two, S-antibody GMC had declined in all groups and remained significantly lower for ChAd-ChAd compared to ChAd-BNT (GMR 5.12 [3.79–6.92]; p<0.001), BNT-ChAd (GMR 4.1 [2.96–5.69]; p<0.001) and BNT-BNT (GMR 6.06 [4.32–8.50]; p<0.001). Previously infected adults had higher S-antibody GMC compared to infection-naïve adults at all time-points and with all vaccine schedules.

Conclusions: These real-world findings demonstrate heterologous schedules with adenoviral-vector and mRNA vaccines are highly immunogenic and may be recommended after a serious adverse reaction to one vaccine product, or to increase programmatic flexibility where vaccine supplies are constrained.

MAH Comments: The CCDS for COVID-19 vaccine Janssen states, "*A booster dose (second dose) of 0.5 mL of TRADENAME may be administered intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. A higher immune response can be expected with a longer interval between the primary vaccination and booster dose*". Based on the heterologous vaccine regimens and extended administration schedule described by the authors, no new safety information is detected at this time.

12. OTHER PERIODIC REPORTS

This section is not applicable as no other 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 hospitalizations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries, regions, and emerging SARS-CoV-2 variants, including variants of concern/variants of interest (VOCs/VOIs), there was a trend towards a decreased protection against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the trial, and this potentially contributes to the observed decrease, although waning protection 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 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.

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

14. LATE-BREAKING INFORMATION

On 25 February 2022, as requested by Brazilian Health Regulatory Agency (ANVISA), an updated local leaflet with the addition of AEs of eye pain, photophobia, and facial paralysis was submitted.

On 08 March 2022, in the final Pharmacovigilance Risk Assessment Committee (PRAC) outcome for the Summary Safety Report (SSR) (EMEA/H/C/005737/MEA/014.8) covering the period of

01 November 2021 to 15 January 2022, based on member state comment in the final SSR AR, PRAC the following was requested:

- a cumulative review for coronary artery disease including myocardial infarction (MI) based on data from clinical trials, post-marketing data, and literature including (age) stratified observed-to-expected (O/E) analyses by 29 April 2022.

- the inclusion of cutaneous small vessel vasculitis as an adverse drug reaction (ADR) in the European Union Product Information (EUPI) by 13 April 2022.

On 23 March 2022, a request from Medicine and Healthcare products Regulatory Agency (MHRA) was received for request for information to the Post-authorisation Measure Bimonthly Summary Safety Report 01 November 2021 to 15 January 2022 concerning reports of TTS following a booster dose with Janssen COVID-19 vaccine. The response was submitted on 30 March 2022.

On 29 March 2022, a grouping of Type II-variations covering the final study reports of 5 non-clinical TTS characterisation studies regarding Janssen COVID-19 vaccine was submitted to EMA. This action item was mentioned as an additional pharmacovigilance activity in the European Union-Risk Management Plan (EU-RMP) version 3.1 (approved on 13 January 2022 via procedure: EMEA/H/C/005737/II/0029).

On 30 March 2022, a grouping of Type II-variations covering the final study reports of 4 clinical TTS characterisation studies regarding Janssen COVID-19 vaccine and an updated EU-RMP (version 4.1) was submitted to EMA. This action item was mentioned as an additional pharmacovigilance activity mentioned in the EU-RMP version 3.1 (approved on 13 January 2022 via procedure: EMEA/H/C/005737/II/0029).

Facial Paralysis

A pooled analysis of the double-blind phases of 5 Company-sponsored trials (COV1001, COV1002, COV2001, COV3001, and COV3009) conducted by the Company at the time of the preparation of this PBRER showed a numerical imbalance for facial paralysis between Ad26.COV2.S (n=4) and placebo (n=1). A cumulative assessment of available safety data has been carried out as a result of this imbalance.

Based on the Company's review of the totality of the data such as biological plausibility, individual case reports from clinical trials and post-marketing spontaneous reports, as well as the numerical imbalance from the pooled clinical trial data analysis, the Company concluded that there is a reasonable possibility that facial paralysis may be associated with Ad26.COV2.S. Therefore the Company will update the CCDS by adding facial paralysis as an ADR with a frequency of Very Rare.

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

15.1. Ongoing Signals

The following signal is currently undergoing evaluation at DLD of this report. Additional details are provided in Appendix 3 of this report.

- IgA Nephropathy: This signal was created due to Regulatory interest based upon a request from the World Health Organization Uppsala Monitoring Center.

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

15.2.1. Serious Hypertension

Request: As requested in EMEA/H/C/PSUSA/00010916/202108: *"It is noted that eighteen serious cases of hypertension (on a total of 30 cases of hypertension) have been reported as of 20 October 2021 in France. The MAH is requested to present a cumulative review focused on serious hypertension, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable."*

MAH Conclusion: The Company has completed the cumulative review and submitted to EMA on 08 February 2022. Based on review of the totality of the data provided in the report, there is insufficient evidence to conclude a causal association between serious hypertension and the use of Ad26.COV2.S vaccine. Key factors supporting this conclusion include that the majority of the cases of serious hypertension were confounded with concurrent or historical risk factors, or anxiety-related reactions, the absence of imbalance from randomised double-blind, placebo-controlled, Phase 3 Clinical Studies involving a large number of subjects, and O/E ratios well below 1 for all age groups and in sensitivity analyses. Hence, the MAH does not consider an update of the product information warranted. The MAH will continue to monitor events of hypertension through routine pharmacovigilance activities.

Additional information on this analysis can be found in Section 2.1 of the Response document titled: Response to the PRAC Rapporteur Request for Supplementary Information: Periodic Safety Update Report (dated 07 February 2022)..

15.2.2. Autoimmune Hepatitis

Request: As requested in EMEA/H/C/PSUSA/00010916/202108: "*the MAH has summarized 6 cases of new onset of autoimmune hepatitis without presenting the cases in depth. The MAH is requested to complete the cases with narratives and present a thorough evaluation of these cases*."

MAH Conclusion: The Company has completed the cumulative review and submitted to EMA on 08 February 2022. None of the 6 cases reporting Autoimmune hepatitis (AIH) met the diagnostic criteria of definitive or probable AIH. Based on the review of evidences from these cases, there was insufficient evidence to conclude that AIH is causally associated with the use of

Ad26.COV2.S vaccine. This topic will continue to be monitored through routine pharmacovigilance activities.

Additional information on this analysis can be found in Section 2.2 of the Response document titled: Response to the PRAC Rapporteur Request for Supplementary Information: Periodic Safety Update Report (dated 07 February 2022).

15.2.3. Acute Macular Neuroretinopathy

Request: As requested in EMEA/H/C/005737/MEA/014.7: *" requested to provide a cumulative review of acute macular neuroretinopathy (AMN) in subjects having been vaccinated with the COVID-19 vaccine Janssen. The MAH also requested to present, if available, any follow-up information for the published case presented in the Bi-monthly SSR (01Nov2021 to 15Jan 2022) (Patel SN, Yonekawa Y. [published online ahead of print, 2021 Sep 24]. Retin Cases Brief Rep. 2021)"*

MAH Conclusion: The Company has completed the cumulative review and submitted to EMA on 08 February 2022. In conclusion, the pathophysiology of AMN is unclear, the aetiologies are uncertain. A causal relationship between AMN and Ad26.COV2.S could not be established based on the totality of data analysed including a cumulative review of cases reported in association with Ad26.COV2.S vaccine, the literature, and the O/E analysis. The Company will continue to monitor this event through routine pharmacovigilance activities.

Additional information on the analysis can be found in Section 9.2.3., Acute Macular Neuroretinopathy, of the Summary Safety Report with a reporting period of 01 November 2021 to 15 January 2022.

15.2.4. Severe Cutaneous Adverse Reactions

Request: The PRAC Final Assessment Report (FAR) for the 25 February 2021 through 24 August 2021 Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202108) received by the Company on 10 March 2022 requested the MAH to address the following in the next PBRER:

"*In (EMEA/H/C/005737/MEA/014.4) covering July 2021 cumulative review of severe cutaneous reactions was provided by the MAH, and an overview was presented in the current PSUR. So far, no concerns have been identified. Nevertheless, an updated cumulative review should be presented with the next PSUR. .*"

MAH Conclusion: This cumulative analysis found insufficient information to associate Severe Cutaneous Adverse Reaction (SCAR) or Erythema Multiforme (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 evaluation can be found in Appendix 8.

15.2.5. Multisystem Inflammatory Syndrome

Request: Per the EMEA/H/C/PSUSA/00010916/202108 (10 March 2022): "*On 2 Sept 2021, a Signal of multisystem inflammatory syndrome (MIS) for COVID-19 vaccines (EPITT ref. No. 19732) was confirmed by the PRAC for all Covid-19 vaccines approved in the EU. The signal on MIS and the evaluation of menstrual disorders have been handled within other procedure and are not commented further in this current PSUSA Assessment.*"

MAH Conclusion: Review of both the interval (25 August 2021 to 24 February 2022) and cumulative cases identified by a search of the Company global safety database has not revealed any new critical safety information on MIS. This event will continue to be closely monitored and reviewed in future PBRERs.

Additional information on the evaluation can be found in Appendix 9.

15.2.6. Flare of Autoimmune Disorders

Request: Based on a signal identified by the Company for flare of autoimmune disorders with the use of COVID-19 vaccine (AD26.COV2.S), the first Ad26.COV2.S PBRER, covering the reporting period of 25 February 2021 to 24 August 2021 included a cumulative safety evaluation on this topic. The results of the analysis which included data from clinical trials, literature, and post-marketing safety data concluded that there was insufficient evidence for a causal association between flare of autoimmune disorders and the use of Ad26.COV2.S.

As part of FAR for the first Ad26.COV2.S PBRER (procedure number EMEA/H/C/PSUSA/00010916/202108), the EMA PRAC Rapporteur requested the following"

"The MAH should present an updated review of exacerbation (flare-up) of pre-existing autoimmune/inflammatory disorders in the next PSUR including data from the scientific literature, clinical studies and the post-marketing cases. A tabulated case summary of cases that have occurred after the cut off for the review within the current PSUSA should be presented, with the following columns: Case ID, Eudravigilance Case ID, PTs, Patient Age, Patient Gender, First Dose to Onset, Medical History, Concomitant Medications, Case Comment, information dose, WHO causality assessment and the reasoning for the causality category. All available information should be presented to help the review, including time from first dose to onset of the flare-up, time from last dose to onset, medical history (including date first symptoms and current medications, if available. In the data presentation and overall discussion, cases from the current review and new cases should be clearly *identified, to facilitate the review."*

MAH Conclusion: Results from the updated analysis of flare of autoimmune/inflammatory diseases, which included a cumulative analysis of cases in the GMS global safety database and a literature review covering the review period of 01 September 2021 to 24 February 2022, did not provide additional information that would change previous conclusions regarding flares of autoimmune disorders and vaccination with Ad26.COV2.S.

Based on the overall analysis of clinical, literature, and post-marketing safety data, there is

insufficient evidence to conclude that flare of autoimmune disorders is causally associated with Ad26.COV.S.

The use of "Use of Ad26.COV2.S in subjects with Autoimmune or Inflammatory Disorders" remains an area of missing information. The Company will continue to closely monitor these cases and discuss them in future PBRERs.

Additional information on this evaluation is found in Appendix 10.

15.2.7. Neuralgic Amyotrophy

Request: As requested in the PRAC FAR for the Ad26.COV2.S PBRER dated 24 February 2021 to 24 August 2021 (EMEA/H/C/PSUSA/00010916/202108) received on 10 March 2022:

"*With the next PSUR, the MAH is requested to present an updated review of cases with neuralgic amyotrophy, with focus on new cases since the current review, and an evaluation, whether the product information needs to be updated.*"

Conclusion: Based on the totality of spontaneous data reviewed from the Company global safety database there is insufficient evidence to establish a causal role of the Ad26.COV2.S vaccine in the occurrence of NA. Although the temporal relationships of the reported events to the vaccine in the 12 cases identified indicate that a causal relationship to the vaccine at individual case level is possible, diagnostic criteria specific to neuralgic amyotrophy was not consistently demonstrated in the cases overall. No change to the product label is warranted.

Key factors to support this conclusion include:

- low number of cases reported cumulatively through 24 February 2022 (n=25) following a total of 44,105,710 doses of Ad26.COV2.S administered worldwide since launch
- none of the 12 cases identified met the van Alfen diagnostic criteria for definitive or probable NA and 33% (4/12) reported a relevant and possible confounding medical history
- many of the cases contained limited information regarding relevant clinical data including supportive diagnostic testing, clinical course, concomitant medications/vaccinations, concurrent conditions/relevant medical history, duration of the event, outcome, and treatment; thus, precluding a thorough medical assessment
- slight increase in the O/E ratio (not statistically significant) did not indicate an increase in the observed to expected count following the administration of Ad26.COV2.S

This topic will continue to be monitored via routine pharmacovigilance activities.

Additional information on the evaluation can be found in Appendix 11.

15.3. Use With Concomitant Vaccination

Introduction

Use with concomitant vaccination is included within the PBRER in line with the Good

Pharmacovigilance Practices (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 different vaccines on the same day.

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 the reporting period of 25 August 2021 to 24 February 2022, 51 (6 medically confirmed and 45 medically unconfirmed) cases reporting the use with concomitant vaccination were identified. Of these cases, 22 serious and 29 nonserious, and reported a total of 226 events (47 serious; 179 nonserious).

Cumulatively, 92 (20 medically confirmed and 72 medically unconfirmed) cases reporting use with concomitant vaccination were identified. Of these cases, 37 were serious and 55 nonserious, and reported a total of 441 events (110 serious; 331 nonserious).

An overview of these cases is presented in Table 15 below.

Table 15: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Period=51	Number of Cases Received Cumulatively=92
Sex	Female	30	52
	Male	20	38
	NR	1	2
Age (Years)[a] **Minimum: 20** **Maximum: 89** **Mean: 51.9** **Median: 51**	18 to 35	8	19
	36 to 50	14	20
	51 to 64	13	28
	≥65	11	19
	Adult	1	1
	NR	4	5
Source	Spontaneous	49	90
	Clinical study (interventional; non-solicited)	1	1
	Clinical study (non-interventional; solicited)	1	1
Country/Territory[b]	United States	35	57
	Netherlands	7	17
	Brazil	3	6
	Spain	2	3

Table 15: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Period=51	Number of Cases Received Cumulatively=92
	Belgium	1	1
	France	1	1
	Germany	1	1
	Poland	1	1
Event Characteristics		**Number of Events=226**	**Number of Events=441**
Seriousness (Event Level)[c]	Nonserious	179	331
	Serious	47	110
Outcome (Event Level)[c]	Resolved	66	126
	Not resolved	39	95
	Resolving	31	89
	Fatal	4	4
	NR	86	127
Concomitant Vaccine Type[d]	Influenza Vaccine	43	58
	Hepatitis B Vaccine	4	10
	Varicella Zoster Vaccine	4	9
	Hepatitis A Vaccine	2	4
	HPV Vaccine	1	1
	Meningococcal Vaccine	1	1
	Pneumococcal Vaccine	1	6
	Rabies Vaccine	1	3
	Tetanus Vaccine	1	5
	Tick-borne Encephalitis Vaccine	1	1

Key: HPV=Human Papillomavirus; NR=Not Reported

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

d: Concomitant vaccines were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 concomitant vaccine.

The frequency distribution of the MedDRA PTs of interest reported in cases reporting use with concomitant vaccination with the use of Ad26.COV2.S is presented in Table 16 below. A single case may contain more than 1 event.

Table 16: Frequency of MedDRA PTs in Cases Reporting Use With Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Vaccination failure	10	0	10	0
Headache	2	6	2	17
COVID-19	1	6	1	6
Dizziness	2	4	2	7
Fatigue	1	5	1	15
Chills	1	4	1	12
Injection site pain	0	5	0	10
Pain in extremity	0	5	2	9
Pyrexia	1	4	1	15
Suspected COVID-19	1	4	1	4

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

a: The MedDRA PTs of interest with frequency ≥5 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 concomitant vaccine.

Of the 51 cases reported during the reporting period of 25 August 2021 to 24 February 2022, in 21 cases the dates of concomitant vaccine administration were specified. However, in the remaining 30 cases no date was specified for the administration of Ad26.COV2.S with concomitant vaccination. An overview of these cases is included in Table 17.

Table 17: Overview of MedDRA PTs in Cases Reporting the Use of Ad26.COV2.S With Concomitant Vaccinations During the Reporting Period (Cases=51)

MedDRA PTs	Number of Events[a]
Cases reporting specified dates of concomitant vaccine administration(n=21)	
Injection site pain	4
Chills	3
Fatigue	3
Headache	3
Vaccination failure	3
Cases reporting unspecified dates of concomitant vaccine administration(n=30)	
Vaccination failure	7
COVID-19	5
Headache	5
Arthralgia	4
Dizziness	4
Fatigue	3
Pain in extremity	3
Pyrexia	3
Sensory disturbance	3
Suspected COVID-19	3

Key: COVID-19=Coronavirus disease-2019; MedDRA=Medical Dictionary for

Table 17: Overview of MedDRA PTs in Cases Reporting the Use of Ad26.COV2.S With Concomitant Vaccinations During the Reporting Period (Cases=51)

MedDRA PTs	Number of Events[a]

Regulatory Activities; n=Number of Events; PT=Preferred Term
a: A single case may report more than 1 MedDRA PT. MedDRA PTs with frequency ≥3 have been presented.

Conclusion

Most of the events reported in subjects receiving Ad26.COV2.S with concomitant vaccines were reactogenic and/or listed for Ad26.COV2.S. No trend in events was observed. Based on review of all the available data, no safety concerns have been identified for use with concomitant vaccines during the reporting period.

15.3.1. Safety Effects of Mixed Schedule

Introduction

Safety effects of mixed schedule concerns a review of data for a potential safety issue after a patient receives different vaccine types against COVID-19 administered on different dates.

Ad26.COV2.S is currently only indicated for primary immunisation against COVID-19. The safety and efficacy of mixed schedules using Ad26.COV2.S has not yet been studied.

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 the reporting period of 25 August 2021 to 24 February 2022, 783 (171 medically confirmed and 612 medically unconfirmed) cases reporting safety effects of mixed schedule were identified. Of these cases, 157 cases were serious and 626 nonserious, and reported a total of 2,962 events (446 serious; 2,516 nonserious).

Cumulatively, 935 (255 medically confirmed and 680 medically unconfirmed) cases reporting safety effects of mixed schedule were identified. Of these cases, 207 were serious and 728 nonserious, and reported a total of 3,532 events (590 serious; 2,942 nonserious).

An overview of the event characteristics of these cases is presented in Table 18 below.

Table 18: Event Characteristics of Cases Involving the Use of Another COVID-19 Vaccine Prior to Vaccination With Ad26.COV2.S

Event Characteristics		Number of Events Reported During the Reporting Period=2,962	Number of Events Received Cumulatively =3,532
Seriousness (Event Level)[a]	Nonserious	2,516	2,942
	Serious	446	590
Outcome (Event Level)[a]	Not resolved	575	704
	Resolved	569	706
	Resolving	276	327
	Fatal	30	48
	Resolved with sequelae	25	25
	NR	1,487	1,722
Concomitant COVID-19 Vaccine Type[b]	BNT 162	388	439
	mRNA 1273	257	306
	ChAdOx1 nCoV-19	45	63
	Sinopharm	3	3
	Sinovac	2	2
	mRNA 2416	1	1
	MRNA encoding the SARS-CoV-2 spike protein, lipid SM-102 spikevax	1	1
	Sanofi	1	1
	Sputnik	1	1
	NR	94	128

Key: COVID 19=Coronavirus disease-2019; NR=Not Reported; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: Seriousness and outcome have been presented for the events. A single case may report more than 1 event.

b: Concomitant COVID-19 vaccines were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 concomitant COVID-19 vaccine.

The frequency distribution of the MedDRA PTs reported in cases reporting use with concomitant vaccination with the use of Ad26.COV2.S is presented in Table 19 below. A single case may contain more than 1 event.

Table 19: Frequency of MedDRA PTs in Cases Reporting Use With Concomitant Vaccination With the Use of Ad26.COV2.S the Use of Another COVID-19 Vaccine Prior to Vaccination With Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	1	219	2	245
Inappropriate schedule of product administration	0	196	0	219
Pyrexia	9	137	14	152
Headache	13	118	15	138
Fatigue	11	107	11	126
Chills	4	101	5	114
Myalgia	5	74	5	87
Injection site pain	3	63	3	69
SARS-CoV-2 test positive	1	62	1	62
COVID-19 immunisation	7	52	7	55
Pain in extremity	4	46	7	57
Malaise	6	42	8	56
Dizziness	2	45	2	48
Pain	3	44	4	49
Nausea	5	39	9	48
Arthralgia	6	37	7	45
Medication error	1	42	1	72
Vaccination failure	41	0	41	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 frequency ≥41 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 event.

Conclusion

The majority of the events reported in patients receiving Ad26.COV2.S with a mixed schedule with other COVID-19 vaccines were reactogenic. No abnormal trend in events was observed compared to the events reported with Ad26.COV2.S alone. Based on review of all the available data, no new significant safety information has been identified for mixed vaccination schedules during the reporting period.

15.4. Vaccination Anxiety-related Reactions

Introduction

Vaccination anxiety-related reactions such as syncope are included within the PBRER in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases). The Council for International Organisations of Medical Sciences (CIOMS)/World Health Organization (WHO) Working Group on Vaccine Pharmacovigilance notes that the types of reactions caused by vaccination anxiety include but are not limited to vasovagal mediated reactions, hyperventilation mediated reactions, and

stress-related psychiatric disorders.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 1,672 (504 medically confirmed and 1,168 medically unconfirmed) cases reporting vaccination anxiety-related reactions were identified. Of these 1,672 cases, 906 were serious and 766 were nonserious, and reported a total of 1,886 events (911 serious; 975 nonserious). Of the 1,672 interval cases, 398 met the criteria as vaccine anxiety-related reactions. Of the 398 cases, 232 were medically confirmed and 295 cases were serious.

Of these 398 cases meeting criteria during the interval, all were from Post-marketing Sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 4,116 (1,167 medically confirmed and 2,949 medically unconfirmed) cases reporting vaccination anxiety-related reactions were identified. Of these 4,116 cases, 2,074 were serious and 2,042 nonserious, and reported a total of 4,649 events (2,013 serious; 2,636 nonserious). Of the 4,116 cumulative cases, 930 met the criteria as vaccine anxiety-related reactions. Of the 930 cases, 547 were medically confirmed and 671 cases were serious.

Of these 930 cumulative cases meeting criteria, all were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

An overview of these 398 (interval) and 930 (cumulative) cases meeting criteria is presented in Table 20 below.

Table 20: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Vaccine Anxiety-Related Reactions

Case Characteristics		Number of Cases Received During the Reporting Period=398	Number of Cases Received Cumulatively=930
Sex	Male	252	576
	Female	138	321
	NR	8	33
Age (Years)[a]	<18	1	4
Minimum: 17	18 to 35	250	528
Maximum:95	36 to 50	77	176
Mean: 34	51 to 64	43	118

Table 20: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Vaccine Anxiety-Related Reactions

Case Characteristics		Number of Cases Received During the Reporting Period=398	Number of Cases Received Cumulatively=930
Median: 29	≥65	7	23
	Adult	3	27
	NR	17	54
Sources	Spontaneous	393	921
	Clinical study (noninterventional, solicited)	5	9
Country/Territory[b]	Portugal	61	186
	Germany	58	79
	Ireland	42	51
	Philippines	39	68
	United States of America	35	143
	Austria	26	39
	Romania	19	26
	France	16	29
	Netherlands	14	72
	South Africa	12	18
	Lao People's Democratic Republic	11	11
	Greece	10	10
	Czech Republic	9	9
	Italy	7	83
	Latvia	6	9
	Spain	6	15
	Poland	5	14
	Estonia	3	8
	Lithuania	3	8
	Moldova, Republic of	3	4
	Brazil	2	9
	Bulgaria	2	2
	Croatia	2	4
	Luxembourg	2	5
	Belgium	1	5
	Egypt	1	1
	Hungary	1	2
	Slovak Republic	1	2
	Vanuatu	1	1

Table 20: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Vaccine Anxiety-Related Reactions

Case Characteristics		Number of Cases Received During the Reporting Period=398	Number of Cases Received Cumulatively=930
Event Characteristics		**Number of Events=487**	**Number of Events=1,127**
Seriousness (Event Level)[c]	Serious	354	757
	Nonserious	132	370
Outcome (Event Level)[c]	Resolved	327	727
	Resolving	46	144
	Not resolved	22	55
	Resolved with sequelae	4	6
	Fatal	1	5
	NR	87	190

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in descending frequency for the current reporting period (25 August 2021 to 24 February 2022).

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

Table 21 describes sex/age reported in 501 cases identified as vaccination anxiety-related reactions.

Table 21: Demographics for Ad26.COV2.S Vaccination Anxiety-Related Reactions Cases Reported During the Reporting Interval (Cases=398)

Sex/Age	Number of Cases
Male	**252**
18 to 29 years	136
30 to 49 years	81
50 to 69 years	25
70+ years	1
Not reported	9
Female	**138**
<18 years	1
18 to 29 years	59
30 to 49 years	43
50 to 69 years	27
70+ years	2
Not reported	6
Age and/or Sex Not Reported[a]	8

Key:

a: Includes the following:
18 to 29 years, no sex (n=2)

Table 21: Demographics for Ad26.COV2.S Vaccination Anxiety-Related Reactions Cases Reported During the Reporting Interval (Cases=398)

Sex/Age	Number of Cases
50 to 69 years, no sex (n=1)	
No age or sex reported (n=5)	

The 398 cases of vaccine-anxiety reactions reported 487 AEs. The vaccine-anxiety AEs identified in these cases are described in Table 22 below:

Table 22: MedDRA Preferred Terms of Interest and Their Outcomes Reported in Cases Identified as Vaccination Anxiety-Related Reactions (Events=487)

MedDRA Preferred Terms	Event Outcome						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	Not Reported	Total
Syncope	0	2	142	3	14	32	**193**
Loss of consciousness	0	7	44	0	7	17	**75**
Presyncope	0	3	56	0	3	10	**72**
Hyperhidrosis	0	6	40	1	8	11	**66**
Pallor	1	0	25	0	4	7	**37**
Anxiety	0	0	6	0	5	5	**16**
Hypotonia	0	1	3	0	2	1	**7**
Unresponsive to stimuli	0	0	4	0	0	1	**5**
Depressed level of consciousness	0	1	1	0	1	1	**4**
Nervousness	0	1	2	0	1	0	**4**
Fear	0	0	0	0	0	2	**2**
Skin discolouration	0	1	1	0	0	0	**2**
Altered state of consciousness	0	0	1	0	0	0	**1**
Hypokinesia	0	0	1	0	0	0	**1**
Seizure like phenomena	0	0	1	0	0	0	**1**
Shock	0	0	0	0	1	0	**1**
Total	**1**	**22**	**327**	**4**	**46**	**87**	**487**

Key: n=Number of Events; MedDRA=Medical Dictionary for Regulatory Activities.

Serious criteria included life-threatening (n=15), hospitalisation (n=41), disability (n=12), death (n=1), and other medically important events (n=286).

The frequency distribution of the MedDRA PTs of interest reported in cases reporting vaccine anxiety-related reactions with the use of Ad26.COV2.S and meeting criteria is presented in Table 23 below. A single case may contain more than 1 EOI.

Table 23: Frequency of MedDRA PTs in Cases Reporting Vaccine Anxiety-Related Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Syncope	193	0	424	0
Loss of consciousness	75	0	161	0
Presyncope	24	48	48	150
Hyperhidrosis	24	42	54	111
Pallor	21	16	38	31
Anxiety	3	13	6	42
Hypotonia	3	4	3	4
Unresponsive to stimuli	5	0	8	0
Depressed level of consciousness	4	0	4	0
Nervousness	0	4	0	12
Fear	0	2	0	5
Skin discolouration	0	2	0	3
Altered state of consciousness	1	0	2	0
Hypokinesia	0	1	1	6
Seizure like phenomena	1	0	2	0
Shock	1	0	5	0

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

a: The MedDRA PTs of interest were sorted by descending frequency for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022. Additional information is found in Section 7., Summaries of Significant Findings from Clinical Trials During the Reporting Interval of this current PBRER.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 398 cases reporting vaccine anxiety-related reactions meeting criteria were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 398 cases reported 355 serious EOI. Of these 398 cases, the most frequently reported country/territory of origin was Portugal (n=61) followed by Germany (n=58), and Ireland (n=42). Of the 398 cases, 252 cases concerned males, 138 females, and 8 had no sex reported. The age range was 17 to 95 years.

The EOI included syncope (n=193), loss of consciousness (n=75), presyncope (n=72), hyperhidrosis (n=66), pallor (n=37), anxiety (n=16), hypotonia (n=7), unresponsive to stimuli (n=5), depressed level of consciousness (n=4), nervousness (n=4), fear (n=2), skin discolouration (n=2), and 1 each for altered state of consciousness, hypokinesia, seizure like phenomena, and shock. The reported mean and median time to onset (TTO) was 2 days and 0 day, respectively. Where reported (n= 400), the outcomes were resolved (n= 327), resolving (n= 46), not resolved (n= 22), resolved with sequelae (n=4), and fatal (n= 1). The event with a fatal outcome was pallor (n= 1).

No ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022.

Fatal Cases

One fatal case was received during the reporting period which was from a Regulatory Authority [LAOFDA] and described a 67-year-old male who experienced dizziness, nausea, fatigue, and pallor 5 minutes after receiving the Ad26.COV2.S, with a fatal outcome occurring on an unspecified date. The events of pallor along with dizziness, nausea, and fatigue occurring 5 minutes following Ad26.COV2.S administration was likely an anxiety-related reaction. However, these events are not expected to lead to a fatal outcome. The causality of Ad.26.COV.2.S causing the patient's death cannot be assessed in this case in the absence of the exact cause of death, latency of the fatal outcome, patient's medical history, concomitant medications, concurrent illness, clinical course of events, and treatment.

Booster Dose

Cumulatively, 6 (1 medically confirmed and 5 medically unconfirmed) cases were identified to have met the criteria as vaccination anxiety-related reactions in individuals who received the booster dose. There were 2 serious and 4 nonserious cases. Of these cases, 3 were heterologous and 3 were homologous. CIOMS II LL is presented in Appendix 7.2.

Conclusion

A review of the cases of anxiety-related reactions identified in the current interval confirmed these are consistent with the known safety data for these events including rapid TTO and typically transient in nature.

Anxiety-related reactions were previously assessed as a signal for Ad26.COV2.S and it has been concluded that these anxiety-reactions to immunisation are a complication of the immunisation process. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance notes that the types of reactions caused by vaccination anxiety include but are not limited to vasovagal mediated reactions, hyperventilation mediated reactions, and stress-related psychiatric disorders.

Based on a review of all available data, no new safety issues were identified for vaccine anxiety-related reactions. Vaccination anxiety-related reactions such as syncope will be discussed in future PBRERs in line with the GVP Module on Vaccines (Product- or Population-Specific

Considerations I: Vaccines for prophylaxis against infectious diseases).

15.5. Vaccine Failure, Lack of Efficacy/Effectiveness

Introduction

Vaccine failure, or lack of efficacy/effectiveness (LOE) is included within the PBRER in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases).

Vaccine-associated enhanced disease (VAED), including Vaccine Associated Enhanced Respiratory Disease (VAERD) is considered an Important Potential Risk in the cRMP for Ad26.COV2.S, based on past experiences in the development of vaccines against Respiratory syncytial virus (RSV), Dengue virus, SARS-CoV-1, and Middle East Respiratory Syndrome Related Coronavirus (MERS-CoV).

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 of 25 August 2021 to 24 February 2022, 7,939 post-marketing cases (6,448 medically confirmed and 1,491 medically unconfirmed) reporting events of vaccine failure, or LOE were identified. Of these 7,939 cases, 6,618 were serious and 1,321 nonserious reporting a total of 13,817 events (11,779 serious, 2,038 nonserious).

Cumulatively, 9,360 (6,914 medically confirmed and 2,446 medically unconfirmed) cases reporting events of vaccine failure, or LOE were identified. Of these 9,360 cases 7,719 were serious and 1,641 nonserious, and reported a total of 15,780 events (13,079 serious; 2,701 nonserious).

All of these cases were reported from post-marketing sources. An overview of these 7,939 (interval) cases and 9,360 (cumulative) cases are presented in Table 24 below.

Table 24: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Period=7,939	Number of Cases Received Cumulatively=9,360
Sex	Male	4,164	4,817
	Female	2,654	3,249
	NR	1,121	1,294
Age (Years)[a]	<18	19	20
	18 to 35	3,459	3,665

Table 24: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Period=7,939	Number of Cases Received Cumulatively=9,360
Minimum: 0.096 **Maximum:101** **Mean: 39.2** **Median: 37**	36 to 50	2,089	2,326
	51 to 64	1,224	1,543
	≥65	533	741
	Adult	20	40
	Elderly	9	9
	Adolescent	1	1
	NR	585	1,015
Sources	Spontaneous	7,888	9,287
	Clinical study (non-interventional, solicited)	51	73
Country/Territory[b]	Austria	4,364	4,435
	United States	1,116	2,030
	Iceland	837	838
	Portugal	471	555
	Germany	309	339
	Philippines	221	257
	France	137	168
	Brazil	54	103
	Estonia	51	54
	Lithuania	49	49
	Belgium	48	58
	Italy	43	77
	Spain	32	63
	Greece	30	33
	Netherlands	26	58
	Czech Republic	17	17
	Poland	13	19
	Taiwan, Province of China	11	11
	Canada	10	10
	Romania	10	13
	South Africa	10	24
	Colombia	8	22
	Switzerland	8	12
	Croatia	6	6
	Lesotho	6	7
	Mexico	6	21
	Bulgaria	5	6
	Hungary	5	5

Table 24: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Period=7,939	Number of Cases Received Cumulatively=9,360
Event Characteristics		**Number of Events=13,817**	**Number of Events=15,780**
Seriousness Criteria (Event Level)	Other medically important condition	10,660	11,578
	Hospitalisation	701	927
	Life-threatening	151	233
	Death	249	309
	Disability	18	32
	NR	2,038	2,701
Seriousness (Event Level)[c]	Serious	11,779	13,079
	Nonserious	2,038	2,701
Outcome (Event Level)[c]	Resolved	789	902
	Not resolved	425	689
	Resolving	334	458
	Fatal	249	309
	Resolved with sequelae	3	6
	NR	12,017	13,416

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in descending frequency (≥5) for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in these 7,939 cases reporting events of vaccine failure, or LOE with the use of Ad26.COV2.S is presented in Table 25 below.

Table 25: Frequency of MedDRA PTs in Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Vaccination failure	6,037	0	6,531	0
COVID-19	4,954	550	5,133	789
SARS-CoV-2 test positive	139	978	185	1,049
Suspected COVID-19	102	381	144	674
COVID-19 pneumonia	143	0	202	0
Therapy non-responder	142	0	464	2
Drug ineffective	126	0	166	3
COVID-19 immunisation	9	55	9	58
SARS-CoV-2 test negative	27	19	68	27
Asymptomatic COVID-19	10	24	15	39

Table 25: Frequency of MedDRA PTs in Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	34	0	42	0

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

a: The MedDRA PTs of interest were sorted by descending frequency for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 MedDRA PT of interest. MedDRA PTs with frequency ≥30 have been presented.

Janssen Sponsored Clinical Studies

During the reporting period, no findings of LOE were identified from Janssen Sponsored Clinical Studies.

Janssen Supported Clinical Studies

During the reporting period, no findings of LOE were identified from Janssen Supported Clinical Studies.

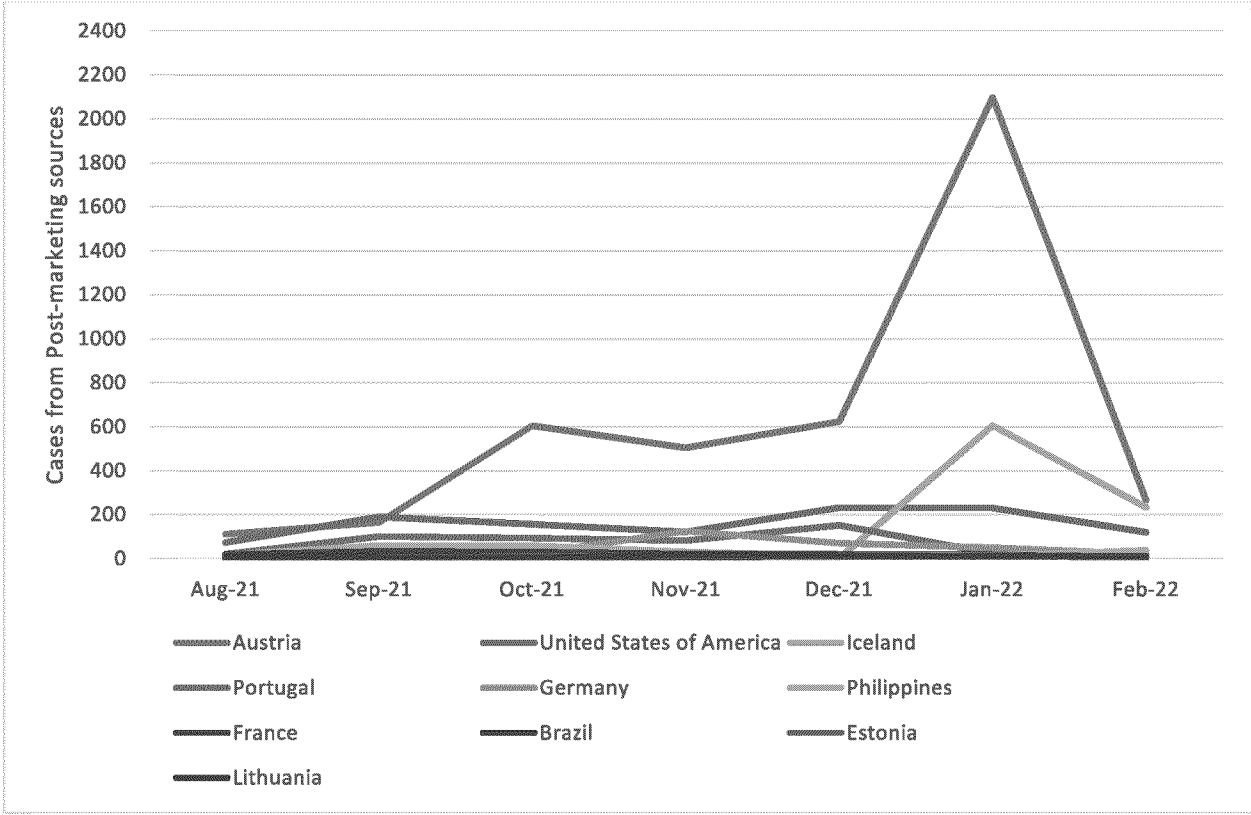
Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 7,939 cases reporting vaccine failure, or LOE were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 7,939 cases reported 11,779 serious EOI. Of these 7,939 cases, the most frequently reported country/territory of origin was Austria (n=4,364) followed by the US (n=1,116), and Iceland (n=837). Of the 7,939 cases, 4,164 cases concerned males, 2,654 females, and 1,121 had no sex reported. The age range was 0.096 to 101 years.

The EOI (≥100) included vaccination failure (n=6,037), COVID-19 (n=5,504), SARS-CoV-2 test positive (n=1,117), suspected COVID-19 (n=483), COVID-19 pneumonia (n=143), therapy non-responder (n=142), and drug ineffective (n=126). Where reported (n=1,800), the outcomes were resolved (n=789), not resolved (n=425), resolving (n=334), fatal (n=249), and resolved with sequelae (n=3).

Figure 1 below depicts the Post-marketing (including spontaneous and solicited) case count from the top 10 countries/territories by month.

Figure 1: Line Graph of Post-marketing Case Count From the Top 10 Countries/Territories by Month



The TTO is presented in Table 26. The mean and median were 94.7 days and 87 days, respectively.

Table 26: Time to Onset in Cases Involving the Use of Ad26.CoV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=7,939)

TTO	Number of Cases
≤14 days	275
>14 days but ≤28 days	305
>28 days	12,066
NR	1,171

Key: TTO=Time To Onset; NR=Not Reported.
a: A single case may report more than 1 MedDRA PT of interest.

Laboratory findings reported are provided in Table 27 below.

Table 27: Laboratory Findings in Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=7,939)

Laboratory Findings[a]	Number of cases
PCR test positive	4,759
COVID-19 test positive	685
Antigen/antibody test Negative	148
Antigen/antibody test positive	80
PCR test negative	59
COVID-19 test negative	53
Antigen/antibody level low	20
NR	2,172

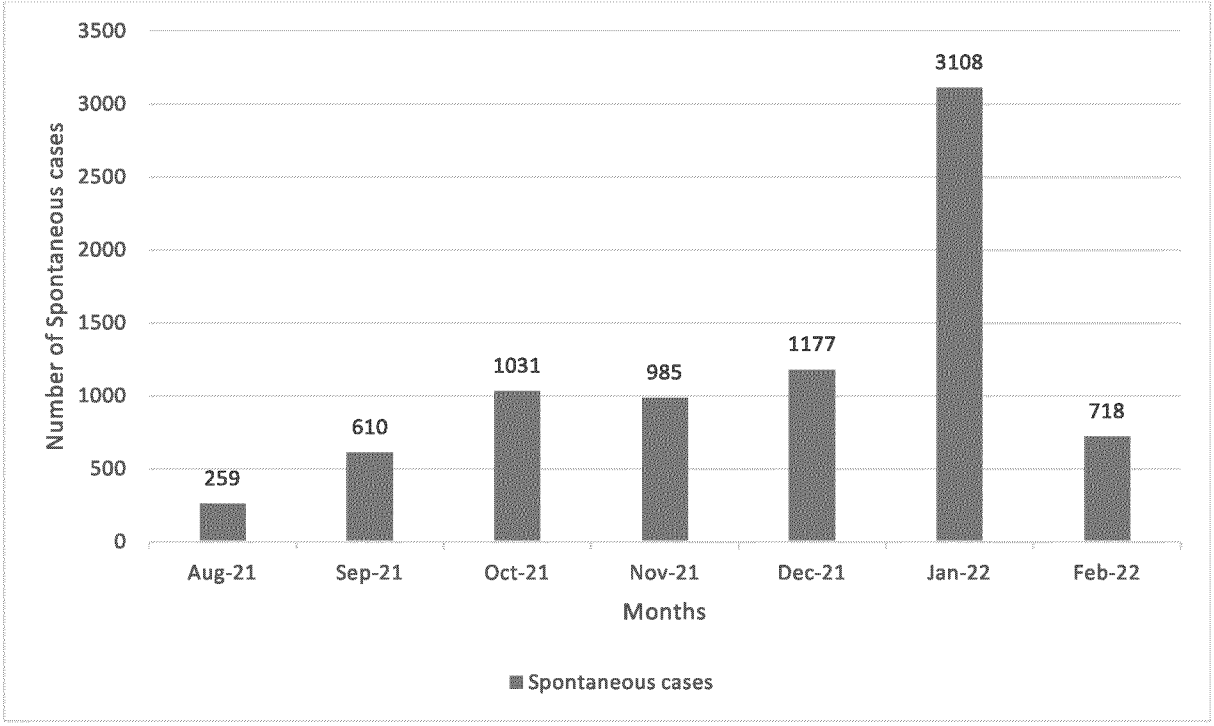
Key: COVID-19=Coronavirus Disease-2019; n=Number of Cases; PCR=Polymerase Chain Reaction; NR=Not Reported.
a: A single case report multiple laboratory findings.

Of the 7,939 post-marketing cases, 542 were reported in the elderly population (≥65). Of these cases, 25 cases reported the presence of the Delta variant, and 16 reported the presence of the Omicron variant.

The Company case definition of vaccination failure is as follows: medically confirmed, TTO >14 days, and positive COVID-19 testing; 112 of the 7,939 cases met this case definition.

Figure 2 depicts the monthly spontaneous case count from August 2021 to February 2022. Figure 2 depicts a peak in an increase in case count in January 2022. The large numbers of cases presenting as LOE in December and January actually reflect persons exposed to the vaccine in December and January.

Figure 2: Histogram of Spontaneous Cases by Month



The events are further sorted by seriousness and their respective outcomes in Table 28 and Table 29 A single case may report more than 1 EOI.

Table 28: Serious MedDRA PTs of Interest and Their Outcomes in Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=11,779)

MedDRA PTs	Number of Event Outcomes						
	Fatal	**Not Resolved**	**Resolved**	**Resolved With Sequelae**	**Resolving**	**NR**	**Total Number of Events[a]**
Vaccination failure	42	75	300	2	106	5,512	6,037
COVID-19	94	62	131	1	70	4,596	4,954
Therapy non-responder	0	7	1	0	0	134	142
SARS-CoV-2 test positive	24	30	30	0	8	47	139
Drug ineffective	2	10	48	0	5	61	126
Suspected COVID-19	32	9	9	0	6	46	102
Thrombosis with thrombocytopenia syndrome	8	4	1	0	1	20	34

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

a: A single case may report more than 1 event of interest. The PTs having frequency ≥30 are presented.

Table 29: Nonserious MedDRA PTs of Interest and Their Outcomes in Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=2,038)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
SARS-CoV-2 test positive	0	13	10	0	8	947	978
COVID-19	0	61	142	0	76	271	550
Suspected COVID-19	0	61	64	0	22	234	381
COVID-19 immunisation	0	0	3	0	2	50	55

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

a: A single case may report more than 1 event of interest. The PTs having frequency ≥30 are presented.

Fatal Cases

Overall, 249 fatal events were reported in 176 cases (see Appendix 7.3.1). Of the 176 fatal cases, 106 concerned males, 54 females, and 16 had no sex reported. The age range was 23 to 97 years. Among patients where age was reported, 4 were in the age range of 18 to 35 years, 22 were in the age range of 36 to 50 years, 40 were in the age range of 51 to 64 years, and 86 were ≥65 years. In 24 patients, the age was not reported. The mean and median TTO reported in these 249 fatal events were 113.4 days and 108 days, respectively.

The frequency distribution of the 249 fatal MedDRA PTs of interest reported in these 176 cases is presented in Table 30 below. A single case may contain more than 1 EOI.

Table 30: Frequency Distribution of Fatal MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Fatal Events=249)

MedDRA PTs	Number of Fatal Events
COVID-19	94
Vaccination failure	42
COVID-19 pneumonia	37
Suspected COVID-19	32
SARS-CoV-2 test positive	24
Thrombosis with thrombocytopenia syndrome	8
SARS-CoV-2 test negative	3
Drug ineffective	2
Exposure to SARS-CoV-2	2
SARS-CoV-2 test	2
COVID-19 immunisation	1
Multisystem inflammatory syndrome in adults	1
SARS-CoV-2 antibody test positive	1

Table 30: Frequency Distribution of Fatal MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Fatal Events=249)

MedDRA PTs	Number of Fatal Events
Total	**249**

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

Booster Dose

Cumulatively, 255 (109 medically confirmed and 146 medically unconfirmed) cases were identified reporting vaccine failure, or LOE in individuals who received the booster dose. There were 129 serious and 126 nonserious cases. Of these cases, 141 were heterologous and 114 were homologous. CIOMS II LL is presented in Appendix 7.3.2.

During the reporting interval a marked increase of cases was received from Austria and Iceland was noted. Interval reports from these 2 countries account for 65.1% of those received during the review interval for vaccination failure/lack of effectiveness. The increase in Austrian reports, which accounts for 54.9% (n=4,364) of the total cases, was found to be related to proactive real-time surveillance by the Health Authority. All laboratories in Austria were obliged by law to report laboratory test results for all notifiable diseases in electronic form and without time lags to the epidemiologic reporting system Epidemiologisches Meldesystem (EMS). These cases from EMS were checked against the electronic vaccination certificate registry as EMS is a central public information system connected to all levels of Austrian health administration. This system is unique to Austria and explains the high reporting rate. Similarly, the increase in reports from Iceland (10.5% of total cases, n=837) was found to be due to the Directorate of Health pulling data regarding confirmed COVID-19 infections which was then submitted in bulk to the Icelandic Medicines Agency who recorded them in the Eudravigilance database. Of note, the cases from Austria and Iceland were received via line listings with minimal case data. However, no new cases received from either country reported events that were fatal, life-threatening, required hospitalisation or were disabling.

The CCDS states that vaccine efficacy (from the ongoing Phase 3 study) against moderate to severe/critical COVID-19 in seronegative individuals was 66.9% at least 14 days post-vaccination and 66.1% at least 28 days post-vaccination. For severe/critical COVID-19 efficacy was 76.7% at least 14 days post-vaccination and 85.4% at least 28 days post-vaccination. In addition it also states immunocompromised persons including individuals receiving immunosuppressant therapy may have a diminished immune response to Ad26.COV2.S.

During this reporting period, 542 cases were reported in the elderly population (≥65). Of these cases, 25 cases reported the presence of the Delta variant, and 16 cases reported the presence of the Omicron variant. Over 44.1 million doses have been administered throughout the world, there

are 7,939 post-marketing reports of vaccine failure; 176 of these are fatal and 870 reported disabilities, hospitalization, or were considered life-threatening. Upon further review, there were only 112 cases meeting the case definition for vaccine failure.

In addition to these active surveillance activities, the Company continuously monitors incoming case reports of COVID-19 following vaccination with Ad26.COV2.S alongside reports of LOE/vaccination failure. As of now, no signal of LOE has been identified from post-authorisation sources. The Company will continue to monitor these case reports and discuss of efficacy/vaccination failure in upcoming periodic safety reports.

On 13 September 2021, the Company was made aware of a report by the French ANSM concerning an overrepresentation of patients vaccinated with Ad26.COV2.S in intensive care for COVID-19 emanating from of 2 regional Pharmacovigilance (PV) centers (Marseille and Tours). The Company is currently evaluating the cases presented in the ANSM report and will include any new findings in future reports.

Conclusion

Based on the review of all the available data, no new significant safety information is observed in the review of vaccination failure cases. No signal suggestive of vaccine failure has been identified with Ad26.COV2.S.

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 higher level term (HLT) of Vaccination site reactions, Injection site reactions, and Administration site reactions NEC. Systemic reactogenicity reactions included PTs of Headache, Pyrexia, Myalgia, Arthralgia, Vomiting, Diarrhoea, Paraesthesia, Hypoaesthesia, Dizziness, Chills, Fatigue, Asthenia, Muscular weakness, and Pain in extremity.

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

During the reporting period of 25 August 2021 to 24 February 2022, 564 (198 medically confirmed and 366 medically unconfirmed) cases reporting reactogenicity were identified. All of the cases were serious and reported a total of 1,371 serious events.

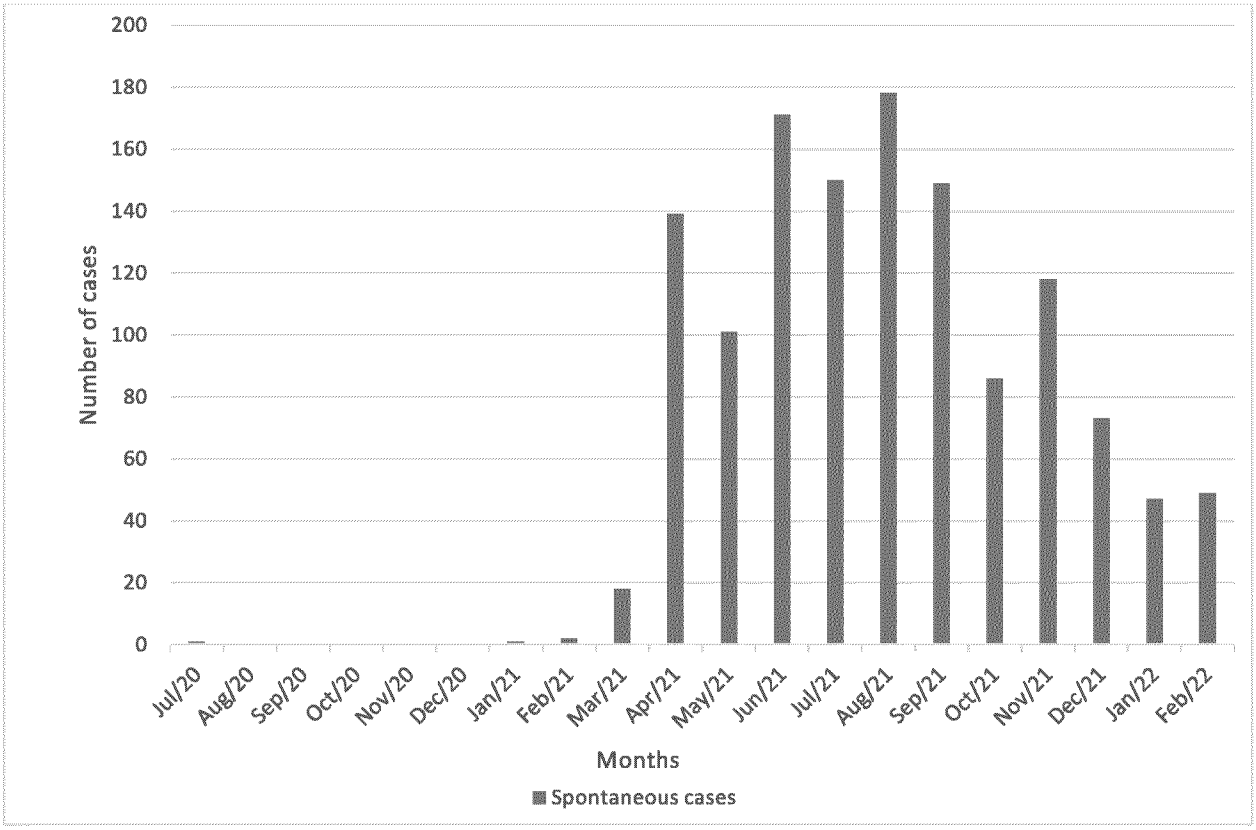
Of these 564 cases during the reporting period of 25 August 2021 to 24 February 2022, 2 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 561 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 1,283 (616 medically confirmed and 667 medically unconfirmed) cases reporting reactogenicity were identified. All of the cases were serious and reported a total of 2,841 serious events.

Of these 1,283 cumulative cases received, 6 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 1,269 from Post-marketing Sources (including spontaneous and solicited cases).

Figure 3 depicts the cumulative number of cases (n=1,283) month-wise.

Figure 3: Histogram of Cumulative Case Reports by Month



An overview of these cases is presented in Table 31 below.

Table 31: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Reporting Period=564	Number of Cases Received Cumulatively=1,283
Sex	Female	305	713
	Male	257	566
	NR	2	4
Age (Years)[a]	<18	1	4
Minimum: 17	18 to 35	188	354
Maximum:88	36 to 50	181	419
Mean: 43	51 to 64	130	317
Median: 43	≥65	49	159
	Adult	3	4
	NR	12	26
Sources	Spontaneous	543	1,242
	Clinical study (non-interventional; solicited)	18	27
	Clinical study (interventional; non-solicited)	3	14
Country/Territory[b]	Germany	136	193
	United States	107	460
	Romania	67	77
	Philippines	40	64
	Italy	21	55
	Austria	20	31
	Ireland	20	29
	Netherlands	18	42
	Greece	17	24
	Korea, Republic of	14	104
	Belgium	11	23
	Croatia	10	15
	South Africa	9	19
	Czech Republic	8	9
	Latvia	7	14
	Portugal	7	24
	Brazil	6	13
	France	5	10
	Spain	5	8
	Estonia	4	4
	Lithuania	4	4
	Poland	4	6
	Switzerland	4	4

Table 31: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Reporting Period=564	Number of Cases Received Cumulatively=1,283
Event Characteristics		**Number of Events=1,371**	**Number of Events=2,841**
Seriousness (Event Level)[c]	Serious	1,371	2,841
Outcome (Event Level)[c]	Not resolved	497	978
	Resolved	301	636
	Resolving	296	507
	Resolved with sequelae	58	67
	Fatal	23	62
	NR	196	591

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥4 have been presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022)

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting reactogenicity with the use of Ad26.COV2.S is presented in Table 32 below. A single case may contain more than 1 EOI.

Table 32: Frequency of MedDRA PTs in Cases Reporting Reactogenicity With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]	Number of Events Received Cumulatively
	Serious	**Serious**
Headache	214	463
Pyrexia	169	365
Fatigue	141	265
Dizziness	138	294
Chills	100	211
Myalgia	97	185
Asthenia	78	136
Paraesthesia	69	123
Hypoaesthesia	67	138
Arthralgia	62	111
Pain in extremity	62	149
Vomiting	46	118
Injection site pain	36	70
Muscular weakness	30	61
Diarrhoea	25	66
Injection site swelling	9	19
Vaccination site pain	8	12

Table 32: Frequency of MedDRA PTs in Cases Reporting Reactogenicity With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]	Number of Events Received Cumulatively
	Serious	Serious
Administration site pain	4	8
Injection site erythema	3	10
Puncture site pain	2	3
Injection site reaction	2	4
Extensive swelling of vaccinated limb	2	3
Injected limb mobility decreased	2	2
Injection site warmth	1	3
Vaccination site mass	1	1
Injection site muscle weakness	1	1
Vaccination site induration	1	1
Injection site pruritus	1	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

The reactogenicity profile of Ad26.COV2.S when used for primary immunisation was established in the pivotal Phase 3 study COV3001. The reactogenicity profile of Ad26.COV2.S when used as an homologous booster was established in the pivotal Phase 3 study COV3009. Reactogenicity was collected as solicited AEs from day 0 to 8 in both studies. Only reactogenicity events assessed as serious by the Investigator were reported to the Global Safety Database.

During the reporting period of 25 August 2021 to 24 February 2022, 2 cases reporting reactogenicity were retrieved from Janssen Sponsored Clinical Studies. One of these cases was from VAC31518COV3001 and concerned a 21-year-old male from [redacted], and the other from VAC31518COV2008 and concerned a 56-year-old female from the [redacted] These 2 cases reported 4 serious EOI. All of the events were assessed as related by both the Sponsor and the Investigator.

Local Reactogenicity Reactions

No cases of serious local reactogenicity were received during the reporting period from Janssen Sponsored Studies.

Systemic Reactogenicity Reactions

Two cases reported systemic reactogenicity reactions. The EOI include asthenia, pyrexia, myalgia, and headache with a seriousness criteria of hospitalisation. The mean and median TTO was 0.2 days and same day, respectively. The outcome was reported as resolved (n=4).

Additionally, cases were reviewed to determine if there were any reported important identified ([eg. TTS] or potential identified risks [(eg. ITP]. No cases were identified.

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting reactogenicity was retrieved from a Janssen Supported Clinical Study. This case was from VAC31518COV3012 and reported 2 serious EOI. Both events were assessed as related by the Company and not related by the Investigator.

Local Reactogenicity Reactions

No cases of serious local reactogenicity were received during the reporting period from Janssen Supported Studies.

Systemic Reactogenicity Reactions

One case reported systemic reactogenicity reactions. The EOI included headache and paraesthesia. The reported TTO was 1 day. The outcome was reported as not resolved (n=2).

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS), or potential identified risks (eg, ITP). No cases were identified

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 561 cases reporting reactogenicity were retrieved from Post-marketing sources (including spontaneous and solicited cases). The 561 cases reported 1,365 serious EOI.

Local Reactogenicity Reactions

Fifty cases reported local reactogenicity reactions. The most frequently reported country/territory of origin was Germany (n=21). Of the 50 cases, 27 concerned females and 23 males with an age range of 18 to 66 years.

The frequency distribution of the 73 MedDRA PTs of interest reported in these 50 cases is presented in Table 33 below. The event outcomes are presented in Table 34. A single case may report more than 1 EOI.

Table 33: Frequency Distribution of MedDRA PTs of Interest Reporting Local Reactogenicity Reactions With the Use of Ad26.COV2.S (Events=73)

MedDRA PTs	Number of Serious Events
Injection site pain	36
Injection site swelling	9
Vaccination site pain	8

Table 33: Frequency Distribution of MedDRA PTs of Interest Reporting Local Reactogenicity Reactions With the Use of Ad26.COV2.S (Events=73)

MedDRA PTs	Number of Serious Events
Administration site pain	4
Injection site erythema	3
Extensive swelling of vaccinated limb	2
Puncture site pain	2
Injected limb mobility decreased	2
Injection site reaction	2
Vaccination site mass	1
Injection site warmth	1
Injection site pruritus	1
Injection site muscle weakness	1
Vaccination site induration	1
Total Events	**73**

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

Table 34: Frequency Distribution of MedDRA PTs of Interest and Their Outcomes for Local Reactogenicity Reactions With the Use of Ad26.COV2.S (Events=73)

MedDRA PT	Number of Event Outcomes					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Injection site pain	9	16	1	9	1	36
Injection site swelling	2	6	0	1	0	9
Vaccination site pain	0	2	0	3	3	8
Administration site pain	1	1	1	0	1	4
Injection site erythema	1	2	0	0	0	3
Puncture site pain	0	1	0	0	1	2
Injection site reaction	1	0	1	0	0	2
Injected limb mobility decreased	2	0	0	0	0	2
Extensive swelling of vaccinated limb	0	1	0	0	1	2
Injection site warmth	0	1	0	0	0	1
Vaccination site induration	0	0	0	0	1	1
Vaccination site mass	0	1	0	0	0	1
Injection site muscle weakness	0	0	0	0	1	1
Injection site pruritus	0	1	0	0	0	1
Total Events	**16**	**32**	**3**	**13**	**9**	**73**

Key: MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term.

The most frequently reported EOI were injection site pain (n=36), and injection site swelling (n=9). The mean and median TTO were 0.7 days and same day, respectively. Where reported (n=64), the outcomes were resolved (n=32), not resolved (n=16), resolving (n=13), and resolved with sequelae (n=3).

Additionally, cases were reviewed to determine if there were any reported important identified (eg. TTS), or potential identified risks (e.g. ITP). Of these 50 cases, anaphylaxis (n=2), GBS (n=2), VTE (n=2), and ITP (n=2) were reported.

Systemic Reactogenicity Reactions

Systemic reactogenicity reactions were reported in 557 cases. The most frequently reported country/territory of origin was Germany (n=135). Of the 557 cases, 254 concerned males, 301 females, and 2 had no sex reported. The age range was 17 to 88 years.

The frequency distribution of the 1,292 MedDRA PTs of interest reported in these 557 cases is presented in Table 35 below. The event outcomes are presented in Table 36. A single case may report more than 1 EOI.

Table 35: Frequency Distribution of MedDRA PTs of Interest Reporting Systemic Reactogenicity With the Use of Ad26.COV2.S (Events=1,292)

MedDRA PTs	Number of Serious Events
Headache	212
Pyrexia	168
Fatigue	141
Dizziness	138
Chills	100
Myalgia	96
Asthenia	77
Paraesthesia	68
Hypoaesthesia	67
Pain in extremity	62
Arthralgia	62
Vomiting	46
Muscular weakness	30
Diarrhoea	25
Total Events	**1,292**

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

Table 36: Frequency Distribution of MedDRA PTs of Interest and Outcomes for Systemic Reactogenicity Reactions With Ad26.CoV2.S (n=1,292)

MedDRA PT	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Headache	2	79	35	9	54	33	212
Pyrexia	9	32	64	7	39	17	168
Fatigue	5	74	16	5	34	7	141
Dizziness	1	52	27	5	32	21	138
Chills	1	24	29	5	25	16	100
Myalgia	0	30	18	4	27	17	96
Asthenia	3	30	14	2	14	14	77

Table 36: Frequency Distribution of MedDRA PTs of Interest and Outcomes for Systemic Reactogenicity Reactions With Ad26.CoV2.S (n=1,292)

MedDRA PT	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Paraesthesia	0	34	13	8	5	8	68
Hypoaesthesia	0	37	14	3	10	3	67
Arthralgia	0	23	8	2	16	13	62
Pain in extremity	0	27	11	1	8	15	62
Vomiting	1	6	11	3	12	13	46
Muscular weakness	0	22	2	0	0	6	30
Diarrhoea	1	9	3	1	7	4	25
Total Events	**23**	**479**	**265**	**55**	**283**	**187**	**1,292**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; NR=Not Reported; PT=Preferred Term.

The most frequently reported EOI were headache (n=212) and pyrexia (n=168). The mean and median TTO were 1.4 days and 1 day, respectively. Where reported (n=1,105), the outcomes were not resolved (n=479), resolving (n=283), resolved (n=265), resolved with sequelae (n=55), and fatal (n=23). There were 16 fatal cases reporting 23 fatal events. The most frequently reported events (n≥3) with a fatal outcome were pyrexia (n=9), fatigue (n=5), and asthenia (n=3).

Additionally, cases were reviewed to determine if there were any reported important identified (e.g. TTS), or potential identified risks (e.g. ITP). Of these 557 cases, anaphylaxis (n=20), GBS (n=20), VTE (n=20), TTS (n=16), VAED (n=1), and ITP (n=20) were reported.

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of reactogenicity.

Fatal Cases

There were 16 fatal cases reporting 23 fatal events. The most frequently reported events (n≥3) with a fatal outcome were pyrexia (n=9), fatigue (n=5), and asthenia (n=3).

Review of the cases, including demographics, outcome, and seriousness received during this reporting period is consistent with what is currently known about reactogenicity reactions.

Booster Dose

Cumulatively, 21 (7 medically confirmed and 14 medically unconfirmed) cases were identified reporting reactogenicity in individuals who received the booster dose. Of these cases, 8 were heterologous and 13 were homologous. All 21 cases were serious. CIOMS II LL is presented in Appendix 7.4.

Conclusion

Local and systemic reactogenicity symptoms are included in the CCDS as common ARs. The review of the cases received during the reporting period have not shown any changes in terms of severity or outcome warranting changes to the prescribing information (PI).

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 PBRER are summarised in Table 37, and are based on the following:

- cRMP (version 3.0; dated 11 August 2021)

Note that the list of safety concerns in the EU RMP and/or cRMP may not be the same as the PBRER based on GVP Module V - Risk Management Systems (Revision 2).

Table 37: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Period

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

16.1.2. At the End of the Reporting Period

The summary of safety concerns (i.e., important identified risks, important potential risks, and missing information) at the end of the reporting period to be included in the PBRER are summarised in Table 38, and are based on the following:

- The cRMP (version 3.0; dated 11 August 2021) was updated to cRMP (version 4.0; dated 09 December 2021) with the removal of the safety concern:
- Important potential risk: Capillary Leak Syndrome (CLS).

VTE was classified an Important Potential Risk in the EU RMP (version 1.4; dated 11 March 2021).

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

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

In the EU RMP (version 2.5, dated 01 December 2021), ITP is characterised as "Thrombocytopenia, including ITP" and is listed as an Important Identified Risk.

VTE has been re-classified as an Important Identified Risk in the EU-RMP version 3.1 (dated 07 January 2022).

For Anaphylaxis, as per PRAC FAR 2022 on the PBRER dated 25 February 2021 to 24 August 2021 (Procedure no.: EMEA/H/C/PSUSA/00010916/202108), the MAH was requested to reclassify "Anaphylaxis" as not "important", and requested to remove it from the summary of safety concerns in the RMP at the next regulatory opportunity.

16.2. Signal Evaluation

16.2.1. Closed Signals

This section presents those signals which were closed within the Signal Tracking System, 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 PV activities or closely monitored and discussed in future PBRERs/PSURs.

16.2.1.1. Closed and Refuted Signals

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

16.2.1.1.1. Vasculitis

This topic was presented in Section 16.2.1.5.1., Vasculitis, in the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021. The conclusion stated that although post-marketing spontaneous reports and isolated cases of biopsy confirmed vasculitis with close temporal relationship following the vaccination of Ad26.COV2.S (eg., <2 weeks) were reported and in consideration of the large number of exposure of Ad26.COV2.S (eg., 33.5 million doses administered), lack of preclinical mechanism of action, no numerical imbalance from the 2 large Phase 3 double-blinded, placebo-controlled clinical trials, as well as the extremely rare post-marketing spontaneous reporting rate compared with the background rates, the MAH considered there is insufficient evidence to conclude a clear causal association between vasculitis and Ad26.COV2.S. The MAH continues to monitor these events and provide updated assessment when additional data become available.

In addition, on 08 March 2022, in the final PRAC outcome for SSR (EMEA/H/C/005737/MEA/014.8) covering the period of 01 November 2021 to 15 January 2022, based on member state comment in the final SSR AR, PRAC the following was requested: the inclusion of cutaneous small vessel vasculitis as an ADR in the EUPI by 13 April 2022.

16.2.1.1.2. Multisystem Inflammatory Syndrome

This topic was presented in Section 14., Late-Breaking Information, in the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021). The conclusion of the analysis stated that there was insufficient evidence to conclude that MIS is causally associated with the use of Ad26.COV2.S.

Additional information can be found in Section 15.2.5, Multisystem Inflammatory Syndrome in the current PBRER reporting period of 25 August 2021 to 24 February 2022.

16.2.1.1.3. Transverse Myelitis

This topic was presented in Sections 16.2.1.5.2., Transverse Myelitis, and Section 16.3.6.4.7., Transverse Myelitis, in the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021. The conclusion stated that based on this review of post-marketing case reports, there is insufficient evidence that encephalitis, encephalomyelitis, and transverse myelitis are associated with the use of Ad26.COV2.S.

Additional information can be found in Section 16.3.6.4.7, Transverse Myelitis and Section 16.3.6.4.3, Encephalitis (Including ADEM) in the current PBRER with a reporting period of 25 August 2021 to 24 February 2022.

16.2.1.1.4. Rhabdomyolysis

Request: On 25 October 2021, a signal was identified for the event of Rhabdomyolysis with the use of COVID-19 VACCINE AD26.COV2.S based on a EMA PRAC request.

Conclusion: A cumulative review was conducted. Based on the review of evidence from cases from interventional clinical studies, post-marketing surveillance data including O/E analysis, and a review of the literature, there was insufficient evidence to conclude that rhabdomyolysis is causally associated with the use of Ad26.COV2.S. Key factors supporting this conclusion included:

- there were no imbalances observed for rhabdomyolysis/myopathy in the interventional clinical trial setting and no serious cases of rhabdomyolysis were observed in the active drug arm of Ad26.COV2.S studies;
- insufficient evidence regarding the causal role of the Ad26.COV2.S vaccine in the occurrence of rhabdomyolysis based on the review of post-marketing data;
- O/E ratio <1 across the broad analysis, >1 in the sensitivity analysis for 18 to 59-year-old in the US, and slightly above 1 (but not statistically significant) when cases with an unlikely diagnosis of rhabdomyolysis per the pre-defined criteria were not included;
- although possible MOA have been suggested, no clear MOA has been established in association with any vaccine. The data yielded from the search of the literature was limited with most cases reporting other contributory factors. Furthermore, while rhabdomyolysis has been reported for a wide spectrum of vaccines over a long period, the total number of published case reports was low. No conclusions could be drawn from the current available published data.

No changes are proposed to the Company core safety information. This topic will continue to be monitored via routine pharmacovigilance activities. The benefit risk profile of the Ad26.COV2.S vaccine remains favorable.

Additional information on the analysis can be found in Appendix 12., Rhabdomyolysis.

16.2.1.2. Closed Signals That are Categorised as Important Identified Risks

No closed signals were categorised as important identified risks.

16.2.1.3. Closed Signals That are Categorised as Important Potential Risks

16.2.1.3.1. Capillary Leak Syndrome

Capillary leak syndrome was removed from the list of safety concerns as indicated Section 14., Late-Breaking Information of the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021. CLS has not been reported during Ad26.COV2.S clinical development. Based on the case reports received from post-marketing experience (6 at the time of the DLD of 04 October 2021, from a total of more than 36 million administered doses of Ad26.COV2.S worldwide), the occurrence of CLS following vaccination with Ad26.COV2.S is extremely rare. The impact for public health is therefore assessed as minimal. The Company has reclassified CLS as an identified risk not considered important. The risk is well characterised and appropriate risk minimisation measures are included in the CCDS, where the Contraindications section states that Ad26.COV2.S is contraindicated in individuals with a history of CLS. There is no reasonable expectation that existing or future pharmacovigilance activities will provide further

characterisation of the safety profile related to CLS.

Additional information on the analysis can be found in Section 16.3.2.4, Capillary Leak Syndrome in the current PBRER reporting period of 25 August 2021 to 24 February 2022.

16.2.1.3.2. Venous Thromboembolism

This topic was presented in Sections 14., Late-Breaking Information, and Section 16.3.2.2., Venous Thromboembolism, in the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021. The conclusion stated that based on the review of the literature, ongoing/completed clinical studies, relevant cases retrieved from the Company global safety database, and an O/E analysis, the Core Company position of VTE as an important potential risk remains unchanged.

Additional information can be found in Section 16.3.2.2, Venous Thromboembolism, in the current PBRER with a reporting period of 25 August 2021 to 24 February 2022.

16.2.1.3.3. Immune Thrombocytopenia

This topic was presented in Sections 14., Late-Breaking Information, and Section 16.3.2.3., Immune Thrombocytopenia, in the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021. The conclusion stated based on the review of the literature, ongoing/completed clinical studies, relevant cases retrieved from the Company global safety database, and an O/E analysis, the Core Company position of ITP as an important potential risk remains unchanged.

Additional information can be found in Section 16.3.2.3, Immune Thrombocytopenia, in the current PBRER with a reporting period of 25 August 2021 to 24 February 2022.

16.2.1.4. Closed Signals That are Identified Risks not Categorised as Important

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

16.2.1.5. Closed Signals That are Potential Risks not Categorised as Important

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

16.3. Evaluation of Risks and New Information

In accordance with Module VII–Periodic Safety Update Reports of the EMA Guideline on GVP the Company collectively assesses new information received during the reporting interval from ICSRs (initial and follow-up cases), clinical studies (if applicable), registries (if applicable), and the literature to determine if there is new information that changes the characterisation of these risks.

Effectiveness of Targeted follow-up questionnaires (TFUQs)

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

activities. During the reporting period, the following TFUQs were used by the Company for Ad26.COV2.S post marketing surveillance:

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

Results

Cumulatively since launch, the Company has issued at least 1 TFUQ for 1,815 cases in the US, of which 184 had a reply received by the Company. In the EEA and Rest of World (ROW), the issuing of TFUQs is carried out by each Local Operating Company; therefore, the Company has no centralised process for the collection of issued/answered TFUQs.

Conclusion

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

Following the re-classification of anaphylaxis as a risk not considered a safety concern, the Company proposes the retirement of the Anaphylaxis/hypersensitivity TFUQ, considering this event is well known adverse reaction and does not require additional characterisation. The Company will retain the questionnaires for TTS, VAED/VAERD, and MIS.

16.3.1. New Information on Important Identified Risks

16.3.1.1. Anaphylaxis

Introduction

Anaphylaxis is as an important identified risk in the cRMP (version 3.0; dated 11 August 2021). Characterisation of this safety concern is provided in Section 16.4, Characterisation of Risks.

As part of the FAR for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202108), the PRAC Rapporteur considered that (a) the occurrence of anaphylaxis following vaccination is well known in clinical practice , (b) that current routine risk minimisation measures are sufficient to mitigate this risk and (c) this risk is no longer considered in need for further characterisation in

ongoing Post-Authorisation Safety Studies. Based on the former, the Rapporteur considered that while anaphylaxis remains an identified risk for the product, as with any other biologicals, it does not have an impact on the benefit/risk balance of the vaccine and therefore suggested anaphylaxis to be reclassified as not "important", and removed from the list of safety concerns.

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 the reporting period of 25 August 2021 to 24 February 2022, 161 (75 medically confirmed and 86 medically unconfirmed) cases reporting anaphylaxis were identified. All of the cases were serious and reported a total of 166 serious events.

Of these 161 cases during the reporting period of 25 August 2021 to 24 February 2022, 3 were reported from Janssen Sponsored Clinical Studies and 158 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 342 (185 medically confirmed and 157 medically unconfirmed) cases reporting anaphylaxis were identified. All of the cases were serious and reported a total of 349 serious events.

Of these 342 cumulative cases received, 4 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 335 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 39 below.

Table 39: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Anaphylaxis

Case Characteristics		Number of Cases Received During the Reporting Period=161	Number of Cases Received Cumulatively=342
Sex	Female	89	170
	Male	65	152
	NR	7	20
Age (Years)[a]	<18	3	3
Minimum: 17	18 to 35	72	120
Maximum:79	36 to 50	43	115
Mean: 37.7	51 to 64	27	57
Median: 36	≥65	7	18
	Adolescent	0	3
	Adult	0	3
	Elderly	1	1

Table 39: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Anaphylaxis

Case Characteristics		Number of Cases Received During the Reporting Period=161	Number of Cases Received Cumulatively=342
	NR	8	22
Sources	Spontaneous	151	325
	Clinical study (non-interventional; solicited)	7	10
	Clinical study (interventional; non-solicited)	3	7
Country/Territory[b]	Germany	58	72
	United States	26	80
	Austria	25	32
	Korea, Republic of	11	59
	Poland	6	13
	Romania	6	8
	Greece	4	7
	Latvia	3	4
	Czech Republic	3	3
	Philippines	3	5
	Ireland	2	9
	South Africa	2	8
	Switzerland	2	2
Event Characteristics		**Number of Events=166**	**Number of Events=349**
Seriousness (Event Level)[c]	Serious	166	349
Outcome (Event Level)[c]	Resolved	78	146
	Resolving	21	39
	Not resolved	16	32
	Fatal	8	23
	Resolved with sequelae	2	2
	NR	41	107

Key: NR=Not Reported; US=United States.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting anaphylaxis with the use of Ad26.COV2.S is presented in Table 40 below. A single case may contain more than 1 EOI.

Table 40: Frequency of MedDRA PTs in Cases Reporting Anaphylaxis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]	Number of Events Received Cumulatively
	Serious	Serious
Circulatory collapse	72	84
Anaphylactic reaction	51	153
Anaphylactic shock	24	54
Shock	11	32
Anaphylactoid reaction	6	24
Procedural shock	1	1
Type I hypersensitivity	1	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by descending order for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 3 cases reporting anaphylaxis were retrieved from Janssen Sponsored Clinical Studies. Of the 3 cases, 1 was from VAC31518COV3001 and 2 were from VAC31518COV3009. These 3 cases reported 3 serious events of interest (EOI). All 3 cases concerned males with the reported age of 39-, 60-, and 79-years, respectively. Of the 3 cases, 2 were reported from the [redacted] and 1 from [redacted]

The EOI included anaphylactic reaction, procedural shock, and shock (n=1 each). The mean and median TTO was 224.7 days and 189 days. None of the EOI were reported on the day of vaccination. The outcome of the 2 EOI was reported as resolved (n=2) and the outcome for 1 EOI was fatal. The Sponsor and Investigator's assessment of the EOI was reported as not related for all EOI. None of these cases reported any additional TTS or venous thromboembolic events.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 158 cases reporting anaphylaxis were retrieved from Post-marketing sources (including spontaneous and solicited cases). These serious 158 cases reported 163 serious EOI. Of these 158 cases, the most frequently reported country/territory of origin was Germany (n=58) followed by Austria (n=25), and the US (n=24). Of the 158 cases, 89 concerned females, 62 males, and 7 had no sex reported. The age range was 17 to 78 years. Of these 158 cases, 107 reported 110 EOI which occurred on the day of vaccination.

The EOI included circulatory collapse (n=72), anaphylactic reaction (n=50), anaphylactic shock (n=24), shock (n=10), anaphylactoid reaction (n=6), and Type I hypersensitivity (n=1). The reported mean and median TTO was 8.8 days and same day, respectively. Where reported (n=122),

the outcomes were resolved (n=76), resolving (n=21), not resolved (n=16), fatal (n=7), and resolved with sequelae (n=2). Of these 158 cases, 9 reported additional venous thromboembolic events.

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of anaphylaxis.

Fatal Cases

The EOI with fatal outcomes included anaphylaxis (n=3) and shock (n=4) which were reported via spontaneous sources (n=6) and clinical study (n=1) that occurred in 6 males and 1 female aged 38 to 79 years. The TTO was reported as "on the same day" (n=2), 1 day (n=2), and 415 days (n=1) following vaccination with Ad26.COV2.S. The TTO was not provided in the remaining 2 cases.

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is consistent with what is currently known about anaphylaxis. Evaluation of the cases and review of safety information from other sources do not support an update of this risk characterisation in Section 16.4, Characterisation of Risks.

Booster Dose

Cumulatively, 8 (3 medically confirmed and 5 medically unconfirmed) cases were identified reporting anaphylaxis in individuals who received the booster dose. All cases were serious. Of these cases, 3 were heterologous and 5 were homologous. CIOMS II LL is presented in Appendix 7.5.

Conclusion

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

Although anaphylaxis associated with vaccines is a potentially life-threatening event requiring medical intervention, it typically occurs at a very low incidence. Moreover, this risk and its management is well known to healthcare professionals, with a negligible public health impact. Therefore, the impact on the risk-benefit balance for the vaccine is considered to be very low. Based on this assessment and feedback received from the PRAC Rapporteur, the Company proposes to take anaphylaxis from the list of safety concerns of the cRMP and continue to monitor risk via routine pharmacovigilance activities.

16.3.1.2. Thrombosis With Thrombocytopenia Syndrome

Introduction

Thrombosis with thrombocytopenia syndrome is an important identified risk in the cRMP (version 3.0; dated 11 August 2021). Characterisation of this safety concern 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.

To ensure that all cases of TTS were identified, the MAH has employed advanced text mining technology by the use of the Self-Service Text Mining Solution (STeMS) tool that has been programmed to specifically identify platelet/thrombocyte count displays within text. As the MAH includes all reported laboratory test results within any case narrative, and those cases downloaded from VAERS or other regulatory databases also generally report this information within the narrative field, potential cases of TTS will be identified allowing the MAH to pinpoint TTS cases and include them within the sub-analysis. An overview of STeMS and the text strings that were applied to the MedDRA SMQ of Embolic and thrombotic events for the purpose of identifying TTS cases and are provided in Appendix 5.

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 46 (39 medically confirmed and 7 medically unconfirmed) cases reporting TTS were identified. Of these cases, 45 were serious and 1 nonserious, and reported a total of 187 events (185 serious; 2 nonserious).

Of these 46 cases during the reporting period of 25 August 2021 to 24 February 2022, 3 were reported from Janssen Sponsored Clinical Studies and 43 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 241 (195 medically confirmed and 46 medically unconfirmed) cases reporting TTS were identified. Of these cases, 239 were serious and 2 nonserious, and reported a total of 903 events (888 serious; 15 nonserious).

Of these 241 cumulative cases received, 12 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 226 from Post-marketing Sources (including spontaneous and solicited cases.

An overview of these cases is presented in Table 41 below.

Table 41: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Reporting Period=46	Number of Cases Received Cumulatively=241
Sex	Male	26	111
	Female	19	124
	NR	1	6
Age (Years)[a]	18 to 35	10	47
Minimum: 20	36 to 50	19	79
Maximum: 73	51 to 64	11	69
Mean: 46.4	≥65	4	38
Median: 48	Adult	0	1
	NR	2	7
Source	Spontaneous	43	225
	Clinical study (non-interventional; solicited)	0	1
	Clinical study (interventional; non-solicited)	3	14
	Clinical study (non-interventional; non-solicited)	0	1
Country/Territory	United States	26	162
	Spain	4	12
	Poland	3	4
	Italy	2	8
	Slovenia	1	2
	France	1	5
	China, PRC	1	1
	Germany	1	14
	Romania	1	1
	Greece	1	4
	South Africa	1	3
	Brazil	1	6
	Czech Republic	1	1
	Netherlands	1	9
	Bulgaria	1	1
Event Characteristics		**Number of Events=187**	**Number of Events=903**
Seriousness (Event Level)[b]	Serious	185	888
	Nonserious	2	15
Outcome (Event Level)[b]	Not resolved	60	340
	Fatal	23	129
	Resolving	15	94
	Resolved	6	81
	Resolved with sequelae	1	4
	NR	82	255

Table 41: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics	Number of Cases Received During the Reporting Period=46	Number of Cases Received Cumulatively=241

Key: NR=Not Reported; PRC= People's Republic of China.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting TTS with the use of Ad26.COV2.S is presented in Table 42 below. A single case may contain more than 1 EOI.

Table 42: Frequency of MedDRA PTs in Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia	20	1	136	3
Thrombosis with thrombocytopenia syndrome	17	0	23	0
Pulmonary embolism	15	0	85	0
Cerebral venous sinus thrombosis	13	0	50	0
Deep vein thrombosis	12	0	53	0
Platelet count decreased	12	0	99	7
Thrombosis	10	0	56	0
Cerebrovascular accident	7	0	17	0
Portal vein thrombosis	4	0	19	0
Ultrasound Doppler abnormal	4	0	16	3
Visceral venous thrombosis	4	0	7	0

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

a: The MedDRA PTs of interest with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

For these 46 cases received during the reporting period, the Company has stratified the cases by age group and sex and applied the TTS working case definitions from BC, CDC, and PRAC (see Table 43).

Table 43: Number of Cases by Age and Sex and Working Case Definitions for Post-marketing Cases Reporting Thrombosis With Thrombocytopenia With the Use of Ad26.COV2.S Vaccine for the Reporting Period (Cases=46; Events=187)

Age Group (Years)	18 to 35		36 to 50		51 to 64		≥65		NR	
Sex	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**NR**
CDC										
Tier 1	1	4	8	5	1	2	0	1	1	1
Tier 2	0	1	0	2	1	0	0	0	0	0
Neither	3	1	1	3	2	5	1	2	0	0
Total	**4**	**6**	**9**	**10**	**4**	**7**	**1**	**3**	**1**	**1**
Brighton Collaboration										
Level 1	1	5	7	8	3	6	0	2	1	1
Level 2	0	0	0	0	0	0	0	0	0	0
Level 3	1	0	1	0	0	0	0	0	0	0
Level 4	0	0	1	1	0	0	0	0	0	0
Level 5	2	1	0	1	1	1	1	1	0	0
Total	**4**	**6**	**9**	**10**	**4**	**7**	**1**	**3**	**1**	**1**
PRAC										
Confirmed	1	2	5	3	1	1	0	1	0	0
Probable	0	1	1	0	0	0	0	1	0	0
Possible	0	3	3	6	2	6	0	0	1	1
Unlikely	0	0	0	1	0	0	0	0	0	0
Criteria not met	3	0	0	0	1	0	1	1	0	0
Total	**4**	**6**	**9**	**10**	**4**	**7**	**1**	**3**	**1**	**1**

Key: CDC=Centres for Disease Control and Prevention; F=Female; M=Male; n=Number of Cases; NR=Not Reported; PRAC=Pharmacovigilance Risk Assessment Committee.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 3 cases reporting TTS were retrieved from Janssen Sponsored Clinical studies. Of the 3 cases, 2 were from VAC31518COV3009 and 1 from VAC31518COV3001. These 3 cases reported 4 EOI (2 serious: 2 nonserious). These 3 cases were reported from [redacted] and [redacted]. Of these 3 cases, 1 concerned a 68-year-old male assessed as BCC level 1/ CDC not applicable / PRAC probable; 1 concerned a 62-year-old female assessed as BCC level 1/ CDC not applicable/ PRAC possible; and the last case concerned a 73-year-old female assessed as BCC level 5/ CDC not applicable/ PRAC criteria not met.

The EOI included cerebrovascular accident, pulmonary embolism, thrombocytopenia, and thrombophlebitis (n=1 each). The mean and median TTO was 201.2 days and 183.5 days, respectively. The outcome of the 4 events was reported as resolved (n=1), resolving (n=1), not resolved (n=1), and resolved with sequelae (n=1). EOI causality was reported as: Sponsor/Investigator assessed as not related (n=3) and related (n=1).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the

reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 43 cases reporting TTS were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 43 cases reported 183 serious EOI. Of these 43 cases, the most frequently reported country/territory of origin was the US (n=26). Of the 43 cases, 25 concerned males, 17 females, and 1 had no sex reported. The age range was 20 to 68 years.

The EOI (n≥10) included thrombocytopenia (n=20), thrombosis with thrombocytopenia syndrome (n=17), pulmonary embolism (n=14), cerebral venous sinus thrombosis (n=13), deep vein thrombosis (n=12), platelet count decreased (n=12), and thrombosis (n=10).; The reported mean and median TTO was 41.5 days and 14 days, respectively. Where reported (n=101), the outcomes were not resolved (n=59), fatal (n=23), resolving (n=14), and resolved (n=5).

There were 6 fatal cases which reported 23 fatal EOI. Of the 6 fatal cases, 2 concerned males and 4 females. The age range was 20 to 51 years. The age among the patients were: 1 in the age range of 18 to 35 years, 4 in the age range of 36 to 50 years, and 1 in the age range of 51 to 64 years. The mean and median TTO reported in these 23 fatal EOI were 10.8 days and 11 days, respectively.

The frequency distribution of the 23 fatal MedDRA PTs of interest reported in these 6 cases is presented in Table 44 below. A single case may contain more than 1 EOI.

Table 44: Frequency Distribution of Fatal MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome (Fatal Events=23)

MedDRA PTs	Number of Fatal Events
Thrombocytopenia	4
Thrombosis with thrombocytopenia syndrome	3
Cerebral venous sinus thrombosis	3
Platelet count decreased	2
Cerebrovascular accident	2
Aortic thrombosis	1
Angiogram cerebral abnormal	1
Pulmonary embolism	1
Renal vein thrombosis	1
Infarction	1
Thrombosis	1
Ovarian vein thrombosis	1
Paresis	1
Peripheral artery thrombosis	1
Total	**23**

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

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of TTS.

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 TTS being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 1 medically confirmed serious heterologous case was identified reporting CVST and thrombocytopenia in a 48-year-old male who received primary vaccination with an mRNA vaccine followed by a booster dose of Ad26.COV2.S 208 days later. The event of CVST occurred approximately 8 months after the primary mRNA vaccination and 12 days after the booster dose with Ad26.COV2.S. The patient had history of hypertension and dyslipidaemia. The case was assessed as BC level 1, CDC Tier 1, and PRAC "possible". The outcome was fatal (unspecified). CIOMS II LL is presented in Appendix 7.6.

Conclusion

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

16.3.1.3. Guillain-Barré Syndrome

Introduction

Guillain-Barré Syndrome (GBS) is an important identified risk in the cRMP (version 3.0, dated 11 August 2021). Characterisation of this safety concern 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 the reporting period of 25 August 2021 to 24 February 2022, 275 (148 medically confirmed and 127 medically unconfirmed) cases reporting GBS were identified. Of these 275 cases, 274 were serious and 1 nonserious, and reported a total of 290 events (289 serious; 1 nonserious).

Of these 275 cases during the reporting period of 25 August 2021 to 24 February 2022, 5 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 269 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 537 (310 medically confirmed and 227 medically unconfirmed) cases reporting GBS were identified. Of these 537 cases, 536 were serious and 1 nonserious, and reported a total of 561 events (560 serious; 1 nonserious).

Of these 537 cumulative cases received, 8 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 527 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 45 below.

Table 45: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Period=275	Number of Cases Received Cumulatively=537
Sex	Male	161	321
	Female	91	186
	NR	23	30
Age (Years)[a]	<18	2	2
Minimum: 17	18 to 35	29	53
Maximum:83	36 to 50	72	142
Mean: 51.8	51 to 64	97	205
Median: 53	≥65	33	74
	Adult	0	3
	Elderly	1	1
	NR	41	57
Sources	Spontaneous	269	527
	Clinical study (interventional; non-solicited)	6	10
Country/Territory[b]	United States	140	306
	Germany	37	65
	Spain	13	20
	France	11	14
	Italy	8	21
	Korea, Republic of	8	18
	Netherlands	7	15
	Philippines	6	7
	Brazil	5	11
	Mexico	5	5
	Portugal	5	10
	Belgium	4	4
	Latvia	4	4
	South Africa	4	5
	Greece	3	3
	Ireland	3	6

Table 45: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Period=275	Number of Cases Received Cumulatively=537
Event Characteristics		**Number of Events=290**	**Number of Events=561**
Seriousness (Event Level)[c]	Serious	289	560
	Nonserious	1	1
Outcome (Event Level)[c]	Not resolved	136	275
	Resolving	50	92
	Resolved	14	30
	Resolved with sequelae	10	17
	Fatal	4	5
	NR	76	142

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥3 have been presented in descending order for the current reporting period (25 August 2021 to 24 February 2022)

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting GBS with the use of Ad26.COV2.S is presented in Table 46 below. A single case may contain more than 1 EOI.

Table 46: Frequency of MedDRA PTs in Cases Reporting Guillain-Barré Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	**Nonserious**	**Serious**	**Nonserious**
Guillain-Barre syndrome	246	0	492	0
Chronic inflammatory demyelinating polyradiculoneuropathy	20	1	28	1
Demyelinating polyneuropathy	9	0	15	0
Miller Fisher syndrome	7	0	13	0
Subacute inflammatory demyelinating polyneuropathy	4	0	8	0
Acute motor-sensory axonal neuropathy	2	0	2	0
Acute motor axonal neuropathy	1	0	1	0

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

a: The MedDRA PTs of interest were sorted by descending order for the reporting period (25 August 2021 to

Table 46: Frequency of MedDRA PTs in Cases Reporting Guillain-Barré Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious

24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 5 cases reporting GBS were retrieved from Janssen Sponsored Clinical Studies. Of the 5 cases, 2 were from VAC31518COV3001 and 3 from VAC31518COV3009. These 5 cases reported 5 EOI (4 serious; 1 nonserious). Of the 5 cases, 1 concerned a female and 4 males. The age range was 52 to 82 years. Of the 5 cases, 2 were reported each from Columbia and Philippines and the remaining case was reported from the US.

The EOI included Guillain-Barre syndrome (n=4), and chronic inflammatory demyelinating polyradiculoneuropathy (n=1). The mean and median TTO was 212 days and 256 days, respectively. The outcome of the 5 EOI was reported as not resolved (n=2), resolved (n=1), resolved with sequelae (n=1), and fatal (n=1). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=4) and related (n=1). This related case concerned a male (unknown age) from the Philippines who experienced a nonserious EOI of chronic inflammatory demyelinating polyradiculoneuropathy. The reported TTO was 258 days, and the outcome was reported as not resolved.

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting GBS was retrieved from Janssen Supported Clinical Study (VAC31518COV3012-Sisonke). This case concerned a 43-year-old [redacted] from South Africa who experienced a serious EOI of GBS. The TTO was not reported and the outcome was reported as not resolved. The Company causality was assessed as related and the Sponsor causality was not reported.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 269 cases reporting GBS were retrieved from Post-marketing sources (including spontaneous and solicited cases). These serious 269 cases reported 284 serious EOI. Of these 269 cases, the most frequently reported country/territory of origin was the US (n=139) followed by Germany (n=37), Spain (n=13), and France (n=11). Of the 269 cases, 90 concerned females, 156 males, and 23 had no sex reported. The age range was 17 to 83 years.

The EOI included Guillain-Barre syndrome (n=241), chronic inflammatory demyelinating polyradiculoneuropathy (n=20), demyelinating polyneuropathy (n=9), Miller Fisher syndrome (n=7), subacute inflammatory demyelinating polyneuropathy (n=4), acute motor-sensory axonal neuropathy (n=2), and acute motor axonal neuropathy (n=1). The reported mean and median TTO

was 27.4 days and 16 days, respectively. Where reported (n=208), the outcomes were not resolved (n=133), resolving (n=50), resolved (n=13), resolved with sequelae (n=9), and fatal (n=3).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of GBS.

Fatal Cases

A total of 3 spontaneous cases reported GBS with a fatal outcome. Of these 3 cases, 1 was received via social media which reported that a male (age unspecified) experienced fatal GBS at an unspecified time following vaccination with Ad26.COV2.S. No additional information was provided concerning the patient's relevant medical history/concurrent conditions/concomitant medications and clinical course. The remaining 2 cases concerned a 57-year-old male with a history of heart failure, myocardial infarction, cerebrovascular accident who was diagnosed with GBS at an unspecified time following vaccination with Ad26.COV2.S and a 69-year-old female with a history of hypertension, alcohol abuse, seizures, and chronic obstructive pulmonary disease who was diagnosed with GBS approximately 1 month following vaccination with Ad26.COV2.S. The fatal outcomes were reported 25 days and 288 days following vaccination with Ad26.COV2.S.

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is consistent with what is currently known about GBS. Evaluation of the cases and review of safety information from other sources do not support an update of this risk characterisation in Section 16.4, Characterisation of Risks.

Booster Dose

Cumulatively, 2 (1 medically confirmed and 1 medically unconfirmed) cases were identified reporting GBS in individuals who received the booster dose. Both cases were serious and heterologous. CIOMS II LL is presented in Appendix 7.7.

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period, it does not change the characterisation of GBS as an important identified risk following immunisation with Ad26.COV2.S.

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 3.0; dated 11 August 2021), Vaccine-Associated Enhanced

Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) is an important potential risk associated with the use of Ad26.CoV2.S. Characterisation of this safety concern 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 the reporting period of 25 August 2021 to 24 February 2022 and cumulatively, 1 medically confirmed serious case reporting VAED was identified and reported 1 serious event from Post-marketing (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting VAED was retrieved from Post-marketing sources (including spontaneous and solicited cases). This case concerned a 40-year-old female who experienced VAED approximately 11 days following the administration of Ad26.COV2.S. No details were provided concerning the patient's clinical course including the outcome of the event, relevant medical history, treatment of the EOI, or concomitant medications.

No ICSR literature cases were received during the reporting period of 25 August 2021 to 24 February 2022.

Evaluation of the case and review of safety information from other sources does not support an update of this risk characterisation in Section 16.4, Characterisation of Risks.

Booster Dose

Cumulatively, no cases were identified reporting VAED including VAERD in individuals who received the booster dose.

Conclusion

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

16.3.2.2. Venous Thromboembolism

Introduction

Venous thromboembolism (VTE) is an important potential risk in the cRMP (version 3.0, dated 11 August 2021). Characterisation of this safety concern 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 the reporting period of 25 August 2021 to 24 February 2022, 1,622 (809 medically confirmed and 813 medically unconfirmed) cases reporting VTE were identified. Of these 1,622 cases, 1,570 were serious and 52 were nonserious, and reported a total of 2,169 events (2,090 serious; 79 nonserious).

Of these 1,622 cases, 81 were reported from Janssen Sponsored Clinical Studies, 7 from Janssen Supported Clinical Studies, and 1,534 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 4,349 (2,594 medically confirmed and 1,755 medically unconfirmed) cases reporting VTE were identified. Of these, 4,232 were serious, and 117 were nonserious, and the cases reported a total of 5,948 events (5,745 serious; 203 nonserious).

Of these 4,349 cumulative cases, 159 were reported from Janssen Sponsored Clinical Studies, 43 from Janssen Supported Clinical Studies, and 4,147 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 47 below.

Table 47: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Period=1,622	Number of Cases Received Cumulatively=4,349
Sex	Male	798	1,949

Table 47: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Period=1,622	Number of Cases Received Cumulatively=4,349
	Female	701	2,193
	NR	123	207
Age (Years)[a]	<18	4	5
Minimum: 13	18 to 35	186	516
Maximum:100	36 to 50	360	1,047
Mean: 53.2	51 to 64	456	1,295
Median: 54	≥65	320	967
	Adult	19	36
	Elderly	5	7
	Neonate	1	1
	NR	271	475
Sources	Spontaneous	1,524	4,131
	Clinical study (interventional; unsolicited	87	200
	Clinical study (noninterventional; solicited	10	16
	Clinical study (noninterventional, unsolicited)	1	2
Country/Territory[b]	United States	1,028	3,266
	Germany	193	292
	France	53	95
	Netherlands	41	99
	Italy	36	90
	South Africa	28	74
	Spain	24	64
	Brazil	20	44
	Philippines	19	27
	Austria	18	25
	Greece	17	28
	Czech Republic	15	17
	Poland	15	30
	Belgium	14	31
	Portugal	14	27
	Ireland	13	21
	Slovenia	10	13
	Latvia	7	9
	Romania	7	9
	Argentina	6	8
	United Kingdom	6	9
	Estonia	5	6
	Egypt	4	4

Table 47: Characteristics of Cases Involving the Use ofAd26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Period=1,622	Number of Cases Received Cumulatively=4,349
	Luxembourg	4	4
	Chile	3	3
	Croatia	3	6
	Lithuania	3	3
	Switzerland	3	3
Event Characteristics		**Number of Events=2,169**	**Number of Events=5,948**
Seriousness (Event Level)[c]	Serious	2,090	5,745
	Nonserious	79	203
Outcome (Event Level)[c]	Not resolved	772	2,470
	Resolved	254	778
	Resolving	244	531
	Fatal	207	429
	Resolved with sequelae	44	65
	NR	648	1675

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥3 have been presented by decreasing order for the current reporting period.

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting VTE with the use of Ad26.COV2.S is presented in Table 48 below. A single case may contain more than 1 EOI.

Table 48: Frequency of MedDRA PTs in Cases Reporting Venous Thromboembolism With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis	480	2	1,313	3
Pulmonary embolism	331	2	930	5
Cerebrovascular accident	274	0	645	1
Deep vein thrombosis	230	13	753	22
Pulmonary thrombosis	73	0	177	0
Hemiparesis	49	0	163	0
Cerebral infarction	44	0	91	0
Cerebral venous sinus thrombosis	41	0	127	0
Thrombosis with thrombocytopenia	34	2	42	2

Table 48: Frequency of MedDRA PTs in Cases Reporting Venous Thromboembolism With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
syndrome				
Hemiplegia	30	0	69	0
Cerebral thrombosis	28	0	80	0
Superficial vein thrombosis	15	9	39	48
Thrombophlebitis	13	11	25	28
Intracardiac thrombus	23	0	42	0
Portal vein thrombosis	20	0	43	0
Venous thrombosis limb	14	5	29	5
Monoplegia	18	0	61	0
Venous thrombosis	14	4	32	9
Cerebral venous thrombosis	16	0	34	0
Pulmonary infarction	13	0	28	0
Infarction	11	0	21	0
Retinal vein occlusion	10	0	22	1
Disseminated intravascular coagulation	9	0	23	0
Embolism	8	1	31	2
Mesenteric vein thrombosis	8	0	19	0
Renal infarct	7	1	13	1
Embolic stroke	7	0	20	0
Haemorrhagic stroke	7	0	30	0
Cerebral ischaemia	6	0	10	0
Diplegia	6	0	19	0
Haemorrhoids thrombosed	3	3	13	6
Paresis	3	3	8	5
Quadriparesis	6	0	7	0
Cerebellar infarction	5	0	8	0
Jugular vein thrombosis	5	0	22	1
Monoparesis	4	1	13	3
Paraparesis	5	0	7	0

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

a: The MedDRA PTs with frequency ≥5 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 81 cases reporting VTE were retrieved from Janssen Sponsored Clinical Studies. Of the 81 cases, 52 were from VAC31518COV3001, 26 from VAC31518COV3009, 1 from VAC31518COV2008, 1 from VAC31518COV2009, and 1 from VAC31518COV3005. Of the 81 cases, the most frequently reported country/territory of origin was the US (n=40). These 81 cases reported 59 serious and 25 nonserious EOI. Of the 81 cases, 47 concerned males, and 34 females. The age range was 30 to 85 years.

The EOI (≥3) included cerebrovascular accident (n=27), pulmonary embolism (n=19), deep vein thrombosis (n=17), and thrombophlebitis and thrombosis (n=3 each). Where reported (n=81), the outcomes were resolving (n=32), resolved (n=23), not resolved (n=11), resolved with sequalae (n=9), and fatal (n=6). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=74), related (n=4); and Sponsor causality assessed as not related with the Investigator causality as related (n=3).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 7 cases reporting VTE were retrieved from Janssen Supported Clinical Studies. Of the 7 cases, 3 were from VAC31518COV3012, 3 from VAC31518COV3021, and 1 from VAC31518COV4007. Of the 7 cases, the most frequently reported country/territory of origin was South Africa (n=6). These 7 cases reported a total of 8 EOI (7 serious;1 nonserious). Of the 7 cases, 5 concerned females and 2 males. The age range was 29 to 80 years.

The EOI included pulmonary embolism (n=5), and deep vein thrombosis, superficial vein thrombosis and portal vein thrombosis (n=1 each). Where reported (n=7), the outcomes were resolving (n=4), resolved (n=2), and not resolved (n=1). The Company and Sponsor's causality assessment of the EOI was reported as not related (n=5); Company causality assessed as related with the Sponsor causality as not related (n=1); Company causality assessed as not related with the Sponsor causality as related (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 1,534 cases reporting VTE were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 1,534 cases reported a total of 2,077 EOI (2,024 serious; 53 nonserious). The most frequently reported country/territory of origin was the US (n=988). Of these 1,534 cases, 749 concerned males, 662 females, and 123 had no sex reported. The age range was 13 to 100 years.

EOI (≥225) included thrombosis (n=479), pulmonary embolism (n=309), cerebrovascular accident (n=247), and deep vein thrombosis (n=225). Where reported (n=1,433), the outcomes were not resolved (n=760), resolved (n=229), resolving (n=208), fatal (n=201), and resolved with sequelae (n=35).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of VTE.

Fatal Cases

Overall, 201 fatal events were reported. The mean and median TTO reported in these 201 fatal events were 56.7 days and 12 days respectively.

Of the 153 fatal cases (see Appendix 7.8.1), 57 concerned males, 74 females, and 22 had no sex reported. The age range was 19 to 95 years. Among patients where age was reported (104/153),

15 were in the age range of 18 to 35 years, 22 were in the age range of 36 to 50 years, 26 were in the age range of 51 to 64 years, and 41 were ≥65 years.

The frequency distribution of the 201 fatal MedDRA PTs of interest reported in these 152 cases is presented in Table 49 below. A single case may contain more than 1 EOI.

Table 49: Frequency Distribution of Fatal MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Venous Thromboembolism (Events=201)

MedDRA PTs	Fatal Outcome
Thrombosis	53
Pulmonary embolism	38
Cerebrovascular accident	23
Cerebral venous sinus thrombosis	10
Deep vein thrombosis	9
Thrombosis with thrombocytopenia syndrome	8
Intracardiac thrombus	6
Pulmonary thrombosis	5
Infarction	4
Hemiparesis	4
Cerebral infarction	4
Angiogram cerebral abnormal	4
Disseminated intravascular coagulation	3
Ultrasound Doppler abnormal	2
Thrombectomy	2
Haemorrhagic stroke	2
Cerebral venous thrombosis	2
Cerebral thrombosis	2
Central venous catheterisation	2
Angiogram abnormal	2
Vena cava thrombosis	1
Thalamic infarction	1
Superior sagittal sinus thrombosis	1
Subclavian vein thrombosis	1
Renal vein thrombosis	1
Portal vein thrombosis	1
Paresis	1
Ovarian vein thrombosis	1
Jugular vein thrombosis	1
Haemorrhagic cerebral infarction	1
Embolism venous	1
Embolic stroke	1
Cerebrovascular disorder	1
Cerebral ischaemia	1
Cerebellar infarction	1
Cavernous sinus thrombosis	1
Total	**201**

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

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness is consistent with what is currently known

about VTE. Evaluation of the cases and review of safety information from other sources do not support an update of VTE in Section 16.4, Characterisation of Risks.

Booster Dose

Cumulatively, 69 (34 medically confirmed and 35 medically unconfirmed) cases were identified reporting VTE in individuals who received the booster dose. There were 68 serious and 1 nonserious cases. Of these cases, 11 were heterologous and 58 were homologous. The CIOMS II LL is presented in Appendix 7.8.2.

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database, there is no change to the current characterisation for VTE. The Company continues to monitor events of VTE and provide updated assessment when additional data becomes available.

16.3.2.3. Immune Thrombocytopenia

Introduction

Immune thrombocytopenia (ITP) is an important potential risk in the cRMP (version 3, dated 11 August 2021). In the EU RMP (version 2.5, dated 01 December 2021), this risk is characterised as "Thrombocytopenia, including ITP" and is listed as an Important Identified Risk. Characterisation of this safety concern 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 a risk window was not reported), an identifiable patient with evidence thrombocytopenia. All cases were reviewed for evidence of thrombocytopenia per the interim BC case definition v 10.16.3 for thrombocytopenia (Brighton Collaboration 2021a); there is no BC criteria for immune thrombocytopenia. Cases are further assessed using a case definition modified from the American Society of Hematology (ASH) (Kelton 2018). It is acknowledged that the threshold appears very high for a case to be able to fulfil the definition of 'confirmed' (Table 50).

Table 50: 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 (2) a low platelet count nadir (<20x10^9/L)	AND (3) 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 (2) a low platelet count nadir (<20x10^9/L)	OR (3) a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause	OR (4) a positive anti-platelet autoantibody test	AND (5) with the exclusion of other causes of thrombocytopenia
Suspect				Reported thrombocytopenia without a reported underlying or associated cause

Key: ASH=American Society of Hematology; IVIG=Intravenous Immunoglobulin.

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 135 (79 medically confirmed and 56 medically unconfirmed) cases reporting ITP were identified. Of these cases, 121 were serious and 14 nonserious, and reported a total of 146 events (126 serious; 20 nonserious).

All 135 cases during the reporting period of 25 August 2021 to 24 February 2022 were reported from Post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 395 (295 medically confirmed and 100 medically unconfirmed) cases reporting ITP were identified. Of these cases, 283 cases were serious and 112 nonserious, and reported a total of 448 events (325 serious; 123 nonserious).

Of these 395 cumulative cases received, 15 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 377 from Post-marketing Sources (including spontaneous and solicited cases.

An overview of these cases is presented in Table 51 below.

Table 51: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Reporting Period=135	Number of Cases Received Cumulatively=395
Sex	Male	69	212
	Female	64	181
	NR	2	2
Age (Years)[a]	18 to 35	22	52
Minimum: 18	36 to 50	31	151
Maximum: 97	51 to 64	47	112
Mean: 52.6	≥65	30	68
Median: 55	Adult	1	3
	NR	4	9
Source	Spontaneous	132	374
	Clinical study (non-interventional; solicited)	3	3
	Clinical study (interventional; non-solicited)	0	17
	Clinical study (non-interventional; non-solicited)	0	1
Country/Territory[b]	United States	68	179
	Germany	17	34
	France	6	12
	Spain	6	20
	Korea, Republic of	5	87
	Netherlands	4	10
	Bulgaria	3	3
	Italy	3	10
	Slovenia	3	3
	Austria	2	5
	Brazil	2	3
	Hungary	2	2
	Philippines	2	3
	Portugal	2	2
	Romania	2	2
Event Characteristics		**Number of Events=146**	**Number of Events=448**
Seriousness (Event Level)[c]	Serious	126	325
	Nonserious	20	123
Outcome (Event Level)[c]	Not resolved	56	141
	Resolved	23	84
	Resolving	22	39
	Fatal	11	19
	Resolved with sequelae	2	4
	NR	32	161

Table 51: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

Case Characteristics	Number of Cases Received During the Reporting Period=135	Number of Cases Received Cumulatively=395

Key: NR=Not Reported
a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).
b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

The frequency distribution of the MedDRA PTs of interest reported in cases reporting ITP with the use of Ad26.COV2.S is presented in Table 52 below. A single case may contain more than 1 EOI.

Table 52: Frequency of MedDRA PTs in Cases Reporting Immune Thrombocytopenia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia	63	0	133	10
Platelet count decreased	30	19	102	35
Immune thrombocytopenia	24	0	70	0
Thrombocytopenic purpura	4	1	11	78
Thrombotic thrombocytopenic purpura	3	0	7	0
Platelet production decreased	1	0	1	0
Thrombosis with thrombocytopenia syndrome	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 135 cases reporting ITP were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 135 cases reported 126 serious EOI. Of these 135 cases, the most frequently reported country/territory of origin was the US (n=68) followed by Germany (n=17), France and Spain (n=6 each). Of the 135 cases, 69 concerned males, 64 females, and 2 had no sex reported. The age range was 18 to 97 years.

The EOI (n>20) included thrombocytopenia, (n=63), platelet count decreased, (n=49), and immune thrombocytopenia, (n=24). The reported mean and median TTO was 52.1 days and 17.5 days, respectively. Where reported (n=114), the outcomes were not resolved (n=56), resolved (n=23), resolving (n=22), fatal (n=11), and resolved with sequelae (n=2). The EOI reported with a fatal outcome were thrombocytopenia (n=7), and platelet count decreased (n=4).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of ITP.

Fatal Cases

Overall, 11 fatal events (see Appendix 7.9.1) were reported in 9 cases concerning 4 males and 7 females. The age range was 28 to 77 years. The age groups of the 9 patients were: 1 in the age range of 18 to 35 years, 2 in the age range of 36 to 50 years, 3 in the age range of 51 to 64 years, and 3 were ≥ 65 years. The PTs were Thrombocytopenia (n=7) and Platelet count decreased (n=4), The mean and median TTO reported in these 11 fatal events were 86 days and 57 days, respectively.

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 ITP being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 7 (5 medically confirmed and 2 medically unconfirmed) cases were identified reporting ITP in individuals who received the booster dose. There were 5 serious and 2 nonserious cases. Of these cases, 2 were heterologous, and 5 were homologous. CIOMS II LL is presented in Appendix 7.9.2.

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database for the current reporting period, ITP is considered an important potential risk. The Company continues to monitor events of ITP and provide updated assessment when additional data becomes available.

16.3.2.4. Capillary Leak Syndrome

Introduction

CLS was removed from the list of safety concerns in the cRMP (version 3.0; dated 11 August 2021) as indicated in Section 14., Late-Breaking Information of the previous PBRER with a reporting period of 25 February 2021 to 24 August 2021:

"*CLS has not been reported during Ad26.COV2.S clinical development. Based on the case reports received from post-marketing experience (6 at the time of the DLD of 04 October 2021, from a total of more than 36 million administered doses of Ad26.COV2.S worldwide), the occurrence of CLS following vaccination with Ad26.COV2.S is extremely rare. The impact for public health is therefore assessed as minimal. The Company has reclassified CLS as an identified risk not considered important. The risk is well characterised and appropriate risk minimisation measures are included in the CCDS, where the Contraindications section states that Ad26.COV2.S is contraindicated in individuals with a history of CLS. There is no reasonable expectation that existing or future pharmacovigilance activities will provide further characterisation of the safety profile related to CLS.*"

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 the reporting period of 25 August 2021 to 24 February 2022, 4 medically confirmed cases reporting CLS were identified. Of these cases, 3 were serious and 1 nonserious, and reported a total of 4 events (3 serious; 1 nonserious).

All 4 cases were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 10 medically confirmed cases reporting CLS were identified. Of these cases, 9 were serious and 1 nonserious, and reported a total of 10 events (9 serious; 1 nonserious).

All 10 cumulative cases received were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

An overview of these cases is presented in Table 53 below.

Table 53: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Capillary Leak Syndrome

Case Characteristics		Number of Cases Received During the Reporting Period=4	Number of Cases Received Cumulatively=10
Sex	Male	3	5
	Female	1	5
Age (Years)[a] **Minimum: 38** **Maximum: 72** **Mean: 56** **Median: 57**	36 to 50	1	2
	51 to 64	2	4
	≥65	1	4
Source	Spontaneous	4	10
Country/Territory[b]	Spain	2	4
	Italy	1	1
	Korea, Republic of	1	1
Event Characteristics		**Number of Events=4**	**Number of Events=10**
Seriousness (Event Level)[c]	Serious	3	9
	Nonserious	1	1
Outcome (Event Level)[c]	Resolving	2	2
	Fatal	0	4
	Not resolved	0	1
	NR	2	3

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting CLS with the use of Ad26.COV2.S is presented in Table 54 below.

Table 54: Frequency of MedDRA PTs in Cases Reporting Capillary Leak Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Capillary leak syndrome	3	0	9	0
Capillary permeability increased	0	1	0	1

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

a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 4 cases reporting CLS were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 4 cases reported 3 serious EOI. Of these 4 cases, the most frequently reported country/territory of origin was Spain (n=2) followed by Italy (n=1), and Korea, Republic of (n=1). Of the 4 cases, 3 concerned males and 1 female. The age range was 38 to 72 years.

The EOI included capillary leak syndrome (n=3) and capillary permeability increased (n=1). The reported mean and median TTO was 4 days and 4 days, respectively. Where reported (n=2), the outcomes were resolving (n=2). No cases with fatal outcome were received during the reporting period.

A single ICSR literature case was received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the characterisation of CLS.

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 risk factors for CLS following administration of Ad26.COV2.S other than a prior medical history of CLS.

Booster Dose

Cumulatively, no cases were identified reporting CLS in individuals who received the booster dose.

Conclusion

CLS has been removed from the list of safety concerns in the Ad26.COV2.S cRMP based on the very rare occurrence of this event and minimal public health impact. Adequate risk minimisation measures are in place and no further actions are warranted. Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database for the current reporting period and cumulatively, no new critical safety information was identified during the reporting period for CLS. The Company will continue to monitor cases of CLS through routine pharmacovigilance

activities.

16.3.3. New Information on Other Identified Risks not Categorised as Important

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

16.3.4. New Information on Other Potential Risks not Categorised as Important

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

16.3.5. Update on Missing Information

16.3.5.1. Use During Pregnancy

Introduction

According to the cRMP (version 3.0; dated 11 August 2021), use during pregnancy is considered missing information for Ad26.COV2.S. This section will contain both information on cases reporting use during pregnancy and use in breastfeeding women.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively and coded to the search criteria provided in Appendix 5.

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 566 (244 medically confirmed and 322 medically unconfirmed) cases reporting use in pregnancy/use in breastfeeding women were identified. Of these 566 cases, 220 were serious and 346 were nonserious, and reported a total of 2,170 events (954 serious; 1,216 nonserious).

Of these 566 interval cases, 40 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy or lactation exposure). In 9 cases, placebo was given and our vaccination of interest was not involved. Additionally, 56 cases reported maternal exposure to vaccine >3 months before conception/pregnancy. Six cases concerned multiple patients without individual patient identifiers. These 111 cases are not discussed further.

Of the remaining 455 cases, 51 were reported from Janssen Sponsored Clinical Studies, 25 from Janssen Supported Clinical Studies, and 379 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 945 (377 medically confirmed and 568 medically unconfirmed) cases reporting use

in pregnancy/use in breastfeeding women were identified. Of these 945 cases, 301 were serious and 644 nonserious, and reported a total of 3,656 events (1,538 serious; 2,118 nonserious). Of the 945 cumulative cases, 81 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy/lactation exposure). In 9 cases, placebo was given and our vaccination of interest was not involved. Additionally, 71 cases reported maternal exposure to vaccine >3 months before conception/pregnancy. Eight cases concerned multiple patients without individual patient identifiers. These 169 cases are not discussed further.

Of the remaining 776 cases included, 98 were reported from Janssen Sponsored Clinical Studies, 28 from Janssen Supported Clinical Studies, and 650 from Post-marketing Sources (including spontaneous and solicited cases).

Pregnancy

During this period, 378 (161 serious and 217 nonserious) cases reporting exposure during pregnancy were identified. Cumulatively, 639 (206 serious and 433 nonserious) cases reported exposure during pregnancy. A frequency distribution of additional AEs in these cases reporting exposure during pregnancy is presented below in Table 55. A single case may contain more than 1 event.

Table 55: Frequency Distribution of Additional Adverse Events in Cases Reporting Exposure During Pregnancy With Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Fatigue	5	57	7	124
Chills	6	55	10	104
Pain in extremity	4	57	4	106
Pyrexia	3	48	7	83
Headache	3	46	5	84
Malaise	5	44	7	75
Myalgia	3	43	5	75
COVID-19	25	9	25	13
Arthralgia	1	20	2	39
Nausea	2	15	3	32
Large for dates baby	1	10	1	10
Pre-eclampsia	9	2	12	2
Gestational hypertension	3	4	3	4
Injection site erythema	1	6	1	8
Dyspnoea	4	2	5	2
Gastrooesophageal reflux disease	4	2	4	2
Heavy menstrual bleeding	4	2	4	3
Injection site pain	0	6	1	13
Neonatal dyspnoea	6	0	7	0
Pain	0	6	0	14

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

a: The additional adverse events with frequency ≥5 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 event.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 51 cases reporting use in pregnancy were retrieved from Janssen Sponsored Clinical Studies. Of the 51 cases, 28 were reported from VAC31518COV3001, 13 from VAC31518COV3009, 4 from VAC31518COV3003, 3 from VAC31518COV2004, 2 from VAC31518COV2001, and 1 from VAC31518COV2008. These 51 cases reported 19 serious events. Of these 51 cases, the most frequently reported country/territory of origin was the US (n=14). Of these 51 cases, 9 concerned males (exposure via partner) and 42 females. The age range was 0.003 to 44 years.

The events (n≥2) included exposure during pregnancy (n=20), maternal exposure before pregnancy (n=15), abortion spontaneous (n=7), pregnancy of partner (n=4), and paternal exposure during pregnancy (n=3), followed by foetal death, foetal exposure during pregnancy, and premature separation of placenta (n=2 each). The mean and median TTO was 162 and 131 days, respectively. Where reported (n=25), the outcomes were resolved (n=20), resolving (n=3), and not resolved and fatal (n=1 each). The event with a fatal outcome was skeletal dysplasia. The Sponsor and Investigator's causality assessment of the events were not related (n=59) and Sponsor assessed as not related with the Investigator causality assessed as not reported (n=5).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 25 reporting use in pregnancy were retrieved from Janssen Supported Clinical Studies. Of the 25 cases, 21 were reported from VAC31518COV3012, 2 were reported from VAC31518COV4007, and 1 each from VAC31518COV2012 and VAC31518COV3021.

These 25 cases reported 24 serious events. Of these 25 cases, the most frequently reported country/territory of origin was South Africa (n=22). All 25 cases concerned females with an age range of 24 to 43 years. The events included COVID-19 (n=21), exposure during pregnancy (n=5), and abortion spontaneous, maternal exposure before pregnancy, medication error, omental haemorrhage, and traumatic liver injury (n=1 each). The mean and median TTO was 213 and 262 days, respectively. Where reported (n=14), the outcomes were resolved (n=6), resolving (n=4), not resolved (n=3), and fatal (n=1). The event with a fatal outcome was COVID-19. The Company and Sponsor's causality assessment of the events was reported as not related (n=27); Company assessed as not related with the Sponsor causality assessed as not reported (n=3) and Company assessed as related with the Sponsor causality assessed as not reported (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 302 cases reporting use in pregnancy were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 302 cases reported 369 serious events. In these 302 cases, the most frequently reported country/territory of origin was the US (n=213) followed by Netherlands (n=15), and Philippines (n=13). Of the 302 cases, 26 concerned males (exposure via partner), 271 females, and

5 did not report sex. The age range was 0.014 to 53 years. The events (n≥10) included exposure during pregnancy (n=181), fatigue (n=62), chills and pain in extremity (n=61 each), pyrexia (n=51), headache and malaise (n=49 each), myalgia (n=46), foetal exposure during pregnancy (n=43), maternal exposure during pregnancy (n=39), abortion spontaneous (n=28), arthralgia (n=21), nausea (n=17), maternal exposure before pregnancy (n=15), COVID-19 and prolonged labour (n=13), large for dates baby (n=11), and pre-eclampsia (n=10).

These 302 cases reported 263 unique pregnancies. The outcomes reported in these 263 pregnancies are provided in Table 56.

Table 56: Unique Pregnancy Outcomes in Post-marketing Cases Reporting Exposure During Pregnancy With Ad26.COV2.S (Cases=263)

Pregnancy Outcomes	Number of Pregnancy Outcomes
Ongoing	66
Live birth without congenital anomalies	56[a]
Spontaneous abortion	30
Live birth with congenital anomalies	6
Ectopic pregnancy	2
NR with congenital anomaly	2
NR	106
Total	**264**

Key: NR=Not Reported
a: One case reported twins; hence, 2 outcomes have been presented for 1 unique case.

Of these 263 unique pregnancies, 90 reported an outcome (including two cases reporting unknown birth outcome with congenital anomaly) and is presented in Table 57.

Table 57: Summary Table of Unique Pregnancy Outcomes (25 August 2021 to 24 February 2022; Cases=263 Unique Pregnancies

Pregnancy Outcome	Prospective Cases Number					Retrospective Cases Number				
	Timing of Exposure in Pregnancy					Timing of Exposure in Pregnancy				
	Before Conception	First Trimester	After First Trimester	During all Pregnancy	Unknown	Before Conception	First Trimester	After First Trimester	During all Pregnancy	Unknown
Ectopic Pregnancy	0	0	0	N/A	0	0	0	0	N/A	1
Spontaneous Abortion[a]	0	2	0	N/A	0	9	11	0	N/A	8
Elective Termination (Foetal Defects)	0	0	0	N/A	0	0	0	0	N/A	0
Elective Termination (no Foetal Defects or Unknown)	0	0	0	N/A	0	0	0	0	N/A	0
Stillbirth With Foetal Defects	0	0	0	N/A	0	0	0	0	N/A	0
Stillbirth Without Foetal Defects	0	0	0	N/A	0	0	0	0	N/A	0
Live Birth With Congenital Anomaly	0	0	5	N/A	0	0	1	0	N/A	0
Live Birth Without Congenital Anomaly[a]	0	7	31	N/A	0	0	0	12	N/A	2
Unknown Birth Outcomes With Congenital Anomaly	0	1	0	N/A	0	0	0	0	0	1
Total	**0**	**10**	**36**	**N/A**	**0**	**9**	**12**	**12**	**N/A**	**12**

Key: NA=Not Applicable

a: Included 4 cases in which no information regarding congenital anomaly was reported.

Use in Breastfeeding Women

The administration of Ad26.COV2.S vaccine to a lactating mother followed by breastfeeding of a baby was reported in 77 (42 medically confirmed and 35 medically unconfirmed) cases. Of these 77 cases, 6 were serious and 71 were nonserious. These 77 cases reported 63 unique lactation cases. Cumulatively, administration of Ad26.COV2.S vaccine to a lactating mother followed by breastfeeding of a baby was reported in 137 (50 medically confirmed and 87 medically unconfirmed) cases. Of these 137 cases, 9 were serious and 128 were nonserious.

A frequency distribution of additional AEs in these cases reporting exposure during breastfeeding is presented below in Table 58.

Table 58: Frequency Distribution of Additional Adverse Events in Cases Reporting Exposure During Breastfeeding With Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	0	6	0	17
Suppressed lactation	1	3	1	4
Malaise	1	2	1	3
Chills	1	1	1	4
Decreased appetite	0	2	0	2
Fatigue	0	2	0	4
Headache	0	2	0	2
Somnolence	0	2	0	3

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The additional adverse events with frequency ≥2 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

There were no literature ICSRs identified during this reporting period.

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

Booster Dose

Cumulatively, 25 (2 medically confirmed and 23 medically unconfirmed) cases were identified reporting pregnancy in individuals who received the booster dose. There were 6 serious and 19 nonserious cases. Of these cases, 17 were heterologous and 8 were homologous. CIOMS II LL is presented in Appendix 7.10.1

No new critical safety information was identified during the reporting period for the missing information of use during pregnancy and use in breastfeeding women. In addition, a COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) semi-annual analysis with reporting dates of 01 June 2021 to 30 November 2021 concluded that there no safety concerns

were identified for either mother or child in cases reporting pregnancy (see Appendix 7.10.2, C-VIPER)

Conclusion

The review identified no trend in events related to exposure during pregnancy. Where reported, most of the cases of pregnancy were still ongoing at the time of reporting. Abnormal pregnancy outcomes represented 13.7% (36/263) of the total unique post-marketing cases, mainly driven by reports of spontaneous abortions in the first trimester of pregnancy (n=13). It is estimated that 10 to 15% of recognised pregnancies result in miscarriage, and 80% of most miscarriages occur during the first trimester of pregnancy. The review of the data did not identify any evidence of an increased risk related to vaccine exposure during pregnancy.

The review of cases that reported exposure via breast milk did not identify any unusual trend in the lactating mother or in exposure to children via breast milk. Most of the events experienced by vaccinated mothers were reactogenic and nonserious.

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

16.3.5.2. Use in Breastfeeding Women

Information on use in breastfeeding women is covered in the section above, Section 16.3.5.1, Use During Pregnancy.

16.3.5.3. Use in Immunocompromised Patients

Introduction

According to the cRMP (version 3.0; dated 11 August 2021), use in immunocompromised patients is considered missing information for Ad26.COV2.S.

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 the reporting period of 25 August 2021 to 24 February 2022, 2,592 (1,188 medically confirmed and 1,404 medically unconfirmed) cases reporting use in immunocompromised patients were identified. Of these cases, 1,591 were serious and 1,001 nonserious, and reported a total of 13,945 events (6,783 serious; 7,162 nonserious).

Of these 2,592 cases during the reporting period of 25 August 2021 to 24 February 2022, 338 were

reported from Janssen Sponsored Clinical Studies, 203 from Janssen Supported Clinical Studies, and 2,051 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 7,158 (2,872 medically confirmed and 4,286 medically unconfirmed) cases reporting use in immunocompromised patients were identified. Of these cases, 3,623 cases were serious and 3,535 nonserious, and reported a total of 41,252 events (15,869 serious; 25,383 nonserious

Of these 7,158 cumulative cases received, 544 were reported from Janssen Sponsored Clinical Studies, 309 from Janssen Supported Clinical Studies, and 6,305 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 59 below.

Table 59: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Case Characteristics		Number of Cases Received During the Reporting Period=2,592	Number of Cases Received Cumulatively=7,158
Sex	Male	890	2,192
	Female	1,648	4,822
	NR	54	144
Age (Years)[a]	0 to 17	6	40
Minimum: 11	18 to 35	394	1,095
Maximum: 98	36 to 50	651	1,750
Mean: 51.3	51 to 64	858	2,323
Median: 52	≥65	438	1,356
	Foetus	0	1
	Adult	47	75
	Elderly	13	16
	NR	185	502
Source	Clinical study (interventional; non-solicited)	543	850
	Spontaneous	1,999	5,857
	Clinical study (non-interventional; non-solicited)	9	16
	Clinical study (non-interventional; solicited)	41	435
Country/Territory[b]	United States	1,403	4,710
	South Africa	270	395
	Netherlands	140	612
	France	133	180
	Brazil	81	139
	Germany	57	108
	Czech Republic	53	59

Table 59: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Case Characteristics		Number of Cases Received During the Reporting Period=2,592	Number of Cases Received Cumulatively=7,158
	Portugal	43	114
	Croatia	40	43
	Austria	39	52
	Spain	35	104
	Belgium	29	76
	Italy	29	119
	Switzerland	24	24
	United Kingdom	21	32
Event Characteristics		**Number of Events=13,945**	**Number of Events=41,252**
Seriousness (Event Level)[c]	Nonserious	7,162	25,383
	Serious	6,783	15,869
Outcome (Event Level)[c]	Not resolved	5,446	15,721
	Resolved	3,457	11,767
	Resolving	1,288	4,051
	Fatal	653	1,185
	Resolved with sequelae	71	154
	NR	3,030	8,374

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥20 have been presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting use in immunocompromised patients with the use of Ad26.COV2.S is presented in Table 60 below. A single case may contain more than 1 event. The most frequently reported events included local and systemic manifestations of reactogenicity. More than half of the cases with the MedDRA PT of COVID-19 (193/338) came from the VAC31518COV3012 Sisonke trial where this event is solicited.

Table 60: Frequency of MedDRA PTs in Cases Reporting Use in Immunocompromised Patients With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	91	334	273	1,592
Pyrexia	107	271	224	1,153
Fatigue	72	288	186	1,314
COVID-19	276	62	387	89

Table 60: Frequency of MedDRA PTs in Cases Reporting Use in Immunocompromised Patients With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pain in extremity	60	174	161	727
Pain	44	175	107	766
Chills	47	172	118	927
Nausea	52	139	141	711
Dizziness	51	140	137	555
Dyspnoea	94	90	235	294
Arthralgia	44	134	111	516
Vaccination failure	169	0	225	0
Malaise	37	130	91	544
Myalgia	34	126	85	618
Asthenia	59	84	109	304

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: MedDRA PTs with frequency ≥143 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

The frequency distribution of the relevant medical history PTs defining use in immunocompromised patients reported in cases is presented in Table 61 below. A single case may contain more than 1 relevant medical history.

Table 61: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Drug hypersensitivity	875	2,894
Asthma	435	1,170
Food allergy	355	1,169
Seasonal allergy	335	1,254
Hypersensitivity	223	510
HIV infection	169	244
Psoriasis	97	187
Rheumatoid arthritis	85	236
Autoimmune thyroiditis	73	198
Rhinitis allergic	66	127
Multiple allergies	60	131
Rubber sensitivity	59	192
Allergy to animal	57	289
Crohn's disease	54	119
Allergy to arthropod sting	49	121
Multiple sclerosis	44	105
Psoriatic arthropathy	41	78

Key: PT=Preferred Term
a: The medical history PTs of interest with frequency ≥40 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022).
b: A single case may report more than 1 relevant medical history.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 338 cases reporting use in immunocompromised patients were retrieved from Janssen Sponsored Clinical Studies. Of the 338 cases, 250 were reported from VAC31518COV3001, 80 from VAC31518COV3009, 4 from VAC31518COV2008, 2 from VAC31518COV1001, and 1 each from VAC31518COV3005 and VAC31518COV3003. These 338 cases reported 405 events (310 serious; 95 nonserious). Of these 338 cases, the most frequently reported country/territory of origin was the US (n=168). Of these 338 cases, 168 concerned males, 169 females, and 1 had no sex reported. The age range was 19 to 92 years.

The events (≥4) included thrombocytopenia (n=60), COVID-19 (n=14), sepsis and platelet count decreased (n=10 each), pulmonary embolism (n=9), osteoarthritis (n=7), nephrolithiasis and acute myocardial infarction (n=5 each), and tibia fracture, prostate cancer, death, gastrointestinal haemorrhage (n=4 each). The mean and median TTO was 233.4 days and 238 days, respectively. Where reported (n=395), the outcomes were resolved (n=213), resolving (n=78), not resolved (n=74), fatal (n=20), and resolved with sequelae (n=10). The Sponsor and Investigator's causality assessment of the events was reported not related (n=393), and as related (n=8). The Sponsor causality assessment as not related; however, the Investigator causality was assessed as related (n=3) and not reported (n=1).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 203 cases reporting use in immunocompromised patients were retrieved from Janssen Supported Clinical Studies. Of the 203 cases, 197 were from VAC31518COV3012, 5 from VAC31518COV3021, and 1 from VAC31518COV4007. These 203 cases reported a total of 205 events (204 serious; 1 nonserious). Of these 203 cases, the most frequently reported country/territory of origin was South Africa (n=202). Of these 203 cases, 32 concerned males and 171 females. The age range was 20 to 74 years.

The events included COVID-19 (n=196), COVID-19 pneumonia (n=2), and immunisation reaction, bradycardia, myocardial infarction, SARS-CoV-2 test positive, superficial vein thrombosis, epilepsy, and gastroenteritis (n=1 each). The mean and median TTO was 197.4 days and 214 days, respectively. Where reported (n=174), the outcomes were resolved (n=101), fatal (n=40), not resolved (n=30), and resolving (n=3). EOI causality was reported as: The Company and Sponsor's causality assessment of the events as not related (n=203), and related (n=1). The Company causality assessment as not related; however, the Sponsor's causality was not reported (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 2,051 cases reporting use in immunocompromised patients were retrieved from Post-marketing sources (including spontaneous

and solicited cases). These 2,051 cases reported a total of 13,335 events (6,269 serious; 7,066 nonserious). Of these 2,051 cases, the most frequently reported country/territory of origin was the US (n=1,235). Of the 2,051 cases, 690 concerned males, 1,308 females, and 53 had no sex reported. The age range was 11 to 98 years.

The events (n≥100) included headache (n=422), pyrexia (n=377), fatigue (n=360), pain in extremity (n=233), chills (n=219), pain (n=218), nausea (n=191), dizziness (n=191), dyspnoea (n=183), arthralgia (n=177), vaccination failure (n=169), malaise (n=167), myalgia (n=160), asthenia (n=143), paraesthesia (n=134), COVID-19 (n=128), feeling abnormal (n=114), hypoaesthesia (n=113), and injection site pain (n=110). The reported mean and median TTO was 50.1 days and 5 days, respectively. Where reported (n=10,346), the outcomes were not resolved (n=5,342), resolved (n=3,143), resolving (n=1,207), fatal (n=593), and resolved with sequelae (n=61).

No ICSR literature cases were retrieved from the search strategy during the reporting period.

Fatal Cases

Of the altogether 2,592 cases received for use in immunocompromised patients, 91 had a fatal outcome. Most frequently reported causes of death were thrombotic and/or haemorrhagic events (n=25), COVID-19 and/or associated events (n=21), or death (n=20).

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 use in immunocompromised patients being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 193 (55 medically confirmed and 138 medically unconfirmed) cases were identified reporting use in immunocompromised patients who received the booster dose. There were 102 nonserious and 91 serious cases. Of these 193 cases, 147 cases were homologous and 46 were heterologous. CIOMS II LL is presented in Appendix 7.11.

Conclusion

Review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period, showed that the safety profile of Ad26.COV2.S. in immunocompromised patients is consistent with the known profile of the vaccine overall. No new safety concern with the use of Ad26.COV2.S. in immunocompromised patients was identified.

16.3.5.4. Use in Patients With Autoimmune or Inflammatory Disorders

Introduction

According to the cRMP (version 3.0; dated 11 August 2021) use in patients with autoimmune or inflammatory disorders is considered missing information for Ad26.COV2.S.

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 the reporting period of 25 August 2021 to 24 February 2022, 1,790 (1,055 medically confirmed and 735 medically unconfirmed) cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these cases, 1,230 were serious and 560 nonserious, and reported a total of 8,706 events (5,200 serious; 3,506 nonserious).

Of these 1,790 cases during the reporting period of 25 August 2021 to 24 February 2022, 300 were reported from Janssen Sponsored Clinical Studies, 292 from Janssen Supported Clinical Studies, and 1,198 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 4,074 (2,071 medically confirmed and 2,003 medically unconfirmed) cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these cases, 2,465 cases were serious and 1,609 nonserious, and reported a total of 21,344 events (10,350 serious; 10,994 nonserious).

Of these 4,074 cumulative cases received, 463 were reported from Janssen Sponsored Clinical Studies, 420 from Janssen Supported Clinical Studies, and 3,191 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 62 below.

Table 62: Characteristics of Cases Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics		Number of Cases Received During the Reporting Period=1,790	Number of Cases Received Cumulatively=4,074
Sex	Female	1,119	2,707
	Male	629	1,270
	NR	42	97
Age (Years)[a]	<18	1	3
Minimum: 11	18 to 35	125	324
	36 to 50	356	796

Table 62: Characteristics of Cases Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics		Number of Cases Received During the Reporting Period=1,790	Number of Cases Received Cumulatively=4,074
Maximum: 98	51 to 64	690	1,504
Mean: 56.4	≥65	427	1,057
Median: 57	Adult	31	53
	Elderly	12	14
	NR	148	323
Source	Spontaneous	1,157	3,060
	Clinical study (interventional; non-solicited)	591	879
	Clinical study (non-interventional; solicited)	34	123
	Clinical study (non-interventional; non-solicited)	8	12
Country/Territory[b]	United States	880	2,545
	South Africa	330	473
	France	100	148
	Brazil	78	121
	Germany	42	72
	Colombia	34	56
	Spain	32	70
	Croatia	26	29
	Czech Republic	24	29
	Netherlands	22	114
	Austria	18	29
	Philippines	18	26
	Argentina	17	24
	Canada	17	18
	Italy	17	63
	Portugal	16	43
	Greece	14	16
	Belgium	10	33
	Estonia	9	10
	Ireland	9	14
	Poland	9	35
	UK	9	16
	Bulgaria	6	7
	Hungary	6	6
	Romania	5	5

Table 62: Characteristics of Cases Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics		Number of Cases Received During the Reporting Period=1,790	Number of Cases Received Cumulatively=4,074
Event Characteristics		**Number of Events=8,706**	**Number of Events=21,344**
Seriousness (Event Level)[c]	Nonserious	3,506	10,994
	Serious	5,200	10,350
Outcome (Event Level)[c]	Not resolved	3,179	8,186
	Resolved	1,981	5,217
	Fatal	720	1,278
	Resolving	657	1,815
	Resolved with sequelae	37	74
	NR	2,132	4,774

Key: NR=Not Reported; UK=United Kingdom.
a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).
b: Countries/Territories with frequency ≥5 have been presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event of interest.

The frequency distribution of the MedDRA PTs reported in these cases is presented in Table 63 below. The most frequently reported events included COVID-19 and local and systemic manifestations of reactogenicity. More than half of the cases with the MedDRA PT of COVID-19 (278/397) came from the VAC31518COV3012 Sisonke trial where this event is solicited.

Table 63: Frequency of the MedDRA PTs Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
COVID-19	364	33	491	42
Headache	50	149	137	597
Pyrexia	64	119	121	435
Fatigue	42	132	91	544
Pain in extremity	33	89	83	348
Pain	30	91	62	365
Vaccination failure	109	0	134	0
Chills	25	70	51	326
Dizziness	34	57	76	212
Dyspnoea	55	36	139	115
Arthralgia	25	61	52	256
Asthenia	39	45	73	157
Nausea	29	49	68	242
Thrombocytopenia	21	53	52	59
Malaise	22	51	48	175

Table 63: Frequency of the MedDRA PTs Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Condition aggravated	39	32	75	74
Feeling abnormal	10	56	22	153
Myalgia	18	46	44	221
Chest pain	41	20	84	68
Paraesthesia	19	37	43	114
SARS-CoV-2 test positive	49	7	60	9
Vomiting	27	26	54	102
Cough	31	21	41	66
Hypoaesthesia	20	32	49	105
Diarrhoea	13	38	26	126
Deep vein thrombosis	45	4	120	6
COVID-19 pneumonia	46	0	65	0
Thrombosis	46	0	157	0
Off label use	0	42	1	58
Pulmonary embolism	42	0	150	1
Death	40	0	80	0

Key: COVID-19=Coronavirus Disease of 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS=Severe Acute Respiratory Syndrome.
a: MedDRA PTs with frequency ≥40 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

The frequency distribution of relevant medical history PTs reported in the 1,790 cases is presented in Table 64 below. A single case may contain more than 1 relevant medical history.

Table 64: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

MedDRA PTs	Number of Medical History PTs Received During the Reporting Period[a]	Number of Medical History PTs Received Cumulatively
Diabetes mellitus	500	1,061
Hypothyroidism	336	751
Arthritis	105	297
Psoriasis	97	187
Rheumatoid arthritis	85	236
Autoimmune thyroiditis	73	198
Neuropathy peripheral	61	146
Crohn's disease	54	119
Thyroid disorder	54	161
Multiple sclerosis	44	105
Psoriatic arthropathy	41	78
Type 1 diabetes mellitus	37	106
Colitis ulcerative	35	75
Autoimmune disorder	34	98
Systemic lupus erythematosus	29	103
Coeliac disease	27	62
Hyperthyroidism	25	56

Table 64: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S in Patients With Autoimmune or Inflammatory Disorders

MedDRA PTs	Number of Medical History PTs Received During the Reporting Period[a]	Number of Medical History PTs Received Cumulatively
Ankylosing spondylitis	21	33
Basedow's disease	18	43
Raynaud's phenomenon	15	38
Rheumatic disorder	14	19

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

a: Medical history PTs with frequency ≥14 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 relevant medical history.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 300 cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Janssen Sponsored Clinical Studies. Of the 300 cases, 236 were from VAC31518COV3001, 57 from VAC31518COV3009, 4 from VAC31518COV2008, 2 from VAC31518COV1001, and 1 from VAC31518COV3005. These 300 cases reported a total of 364 events (269 serious; 95 nonserious). Of these 300 cases, the most frequently reported country/territory of origin was the US (n=147) followed by Brazil (n=54). Of these cases, 157 concerned females, 142 males, and 1 had no sex reported. The age range was from 26 to 90 years.

The top 5 events included thrombocytopenia (n=53), COVID-19 (n=14), platelet count decreased (n=11), sepsis (n=7), osteoarthritis (n=6), pulmonary embolism (n=6), and deep vein thrombosis (n=5). The mean and median TTO was 250.6 days and 268 days, respectively. Where reported (n=356), the outcomes were resolved (n=171), resolving (n=99), not resolved (n=54), fatal (n=24), and resolved with sequelae (n=8). The Sponsor and Investigator's causality assessment of the events was reported as not related (n= 357), and related (n= 4 events). The Sponsor and Investigator's causality assessment of the events was reported as not related/related (n=2), and not related/not reported (n=1).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 292 cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Janssen Supported Clinical Studies. Of the 292 cases, 283 were from VAC31518COV3012, 8 from VAC31518COV3021, and 1 from VAC31518COV4007. These 292 cases reported a total of 294 events (292 serious; 2 nonserious). The countries/territories of origin in these cases were South Africa (n=291), and Brazil (n=1). Of these cases, 211 concerned females and 81 males. The age range was 28 to 81 years.

The events reported in these cases were COVID-19 (n=283), and anaemia, appendicitis, Bell's palsy, COVID-19 pneumonia, immunisation reaction, maternal exposure before pregnancy,

medication error, myocardial infarction, pneumonia, psoriatic arthropathy, and seizure (n=1 each). The mean and median TTO was 172.8 days and 159 days, respectively. Where reported (n=267), the outcomes were resolved (n=162), fatal (n=62), not resolved (n=39), and resolving (n=4). The Company and Sponsor's causality assessment of the events was reported not related for 288 events and related for 1 event. The Company and Sponsor's causality assessment of the events was reported as not related/possible (n=1), not related/not reported (n=1), not reported/not related (n=1), related/not reported (n=1), and related/possible (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 1,198 cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 1,198 cases reported a total of 8,048 events (4,639 serious; 3,409 nonserious). The most frequently reported country/territory of origin was the US (n=733) followed by France (n=98), and Germany (n=42). Of the 1,198 cases, 751 concerned females, 405 males, and 41 had no sex reported. The age range was 11 to 98 years.

The most frequently reported events (n≥100) represented acknowledged local and systemic reactogenicity to Ad26.COV2.S such as headache (n=195), pyrexia (n=182), fatigue (n=174), pain in extremity (n=122), pain (n=121), as well as vaccination failure (n=109), and COVID-19 (n=100). The reported mean and median TTO was 76.6 days and 18 days, respectively. Where reported (n=5,951), the outcomes were fatal (n=634), not resolved (n=3,086), resolved (n=1,648), resolved with sequelae (n=29), and resolving (n=554). The most frequently reported events (n ≥10) with a fatal outcome were death (n=36), COVID-19 (n=19), SARS-COV-2 test positive (n=12), COVID-19 pneumonia (n=11) and dyspnoea (n=11).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the safety profile of the vaccine in this patient population.

Overall, the review of the cases, including demographics, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is consistent with the safety profile of Ad26.COV2.S in the overall population. Evaluation of the cases and review of safety information from other sources did not identify a new safety concern.

During the reporting period, a cumulative evaluation was conducted on flares of autoimmune disorders. Additional information on this analysis can be found in Section 15.2.6, Flare of Autoimmune Disorders.

Booster Dose

Cumulatively, 125 (41 medically confirmed and 84 medically unconfirmed) cases were identified reporting events in patients with autoimmune or inflammatory disorders who received the booster dose. There were 49 serious and 76 nonserious cases. Of these cases, 24 were heterologous and

101 were homologous. CIOMS II LL is presented in Appendix 7.12.

Conclusion

Review of the (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period showed that the safety profile of Ad26.COV2.S in patients with underlying autoimmune or inflammatory disorders is consistent with the known profile of the vaccine overall. No new safety concern with the use of Ad26.COV2.S in patients with autoimmune or inflammatory disorders was identified.

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

Introduction

According to the cRMP (version 3.0, dated 11 August 2021), use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) is considered missing information for Ad26.COV2.S.

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, which defines frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 91 (69 medically confirmed and 22 medically unconfirmed) cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these cases, 24 were serious and 67 nonserious, and reported a total of 250 events (113 serious; 137 nonserious).

Of these 91 cases during the reporting period of 25 August 2021 to 24 February 2022, 58 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 32 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 173 (110 medically confirmed and 63 medically unconfirmed) cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these cases, 103 cases were nonserious and 70 serious, and reported a total of 552 events (241 serious; 311 nonserious).

Of these 173 cumulative cases received, 78 were reported from Janssen Sponsored Clinical Studies, 5 from Janssen Supported Clinical Studies, and 90 from Post-marketing Sources

(including spontaneous and solicited cases).

An overview of these cases is presented in Table 65 below.

Table 65: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Case Characteristics		Number of Cases Received During the Reporting Period=91	Number of Cases Received Cumulatively=173
Sex	Male	59	100
	Female	31	71
	NR	1	2
Age (Years)[a]	18 to 35	4	13
Minimum: 21	36 to 50	10	35
Maximum: 96	51 to 64	14	29
Mean: 60.2	≥65	20	43
Median: 62	Elderly	1	1
	NR	42	52
Source	Clinical study (interventional; non-solicited)	58	83
	Spontaneous	32	89
	Clinical study (non-interventional; non-solicited)	1	1
Country/Territory[b]	Brazil	34	37
	United States	22	69
	Colombia	8	10
	Greece	6	7
	Germany	5	12
	South Africa	4	13
	Belgium	3	4
	France	2	2
	Chile	1	1
	Ireland	1	1
	Netherlands	1	3
	Peru	1	2
	Poland	1	2
	Puerto Rico	1	2
	Spain	1	3
Event Characteristics		**Number of Events=250**	**Number of Events=552**
Seriousness (Event Level)[c]	Nonserious	137	311
	Serious	113	241
Outcome (Event Level)[c]	Not resolved	68	133
	Resolved	52	139
	Resolving	25	60
	Fatal	3	19

Table 65: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Case Characteristics		Number of Cases Received During the Reporting Period=91	Number of Cases Received Cumulatively=173
	NR	102	200

Key: COPD=Chronic Obstructive Pulmonary Disease; NR=Not Reported.
a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).
b: Countries/Territories are listed in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

The frequency distribution of the MedDRA PTs reported in cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) with the use of Ad26.COV2.S is presented in Table 66 below. A single case may contain more than 1 event.

Table 66: Frequency of MedDRA PTs in Cases Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders) With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia	1	38	6	42
Platelet count decreased	1	6	2	8
Expired product administered	0	5	0	5
Deep vein thrombosis	2	2	12	2
Dyspnoea	3	1	4	2
Pain in extremity	1	3	3	9
Confusional state	1	2	2	3
Dizziness	0	3	0	4
Headache	1	2	2	17
Muscular weakness	1	2	1	2
Pulmonary embolism	3	0	8	0
Pyrexia	1	2	2	9

Key: COPD= Chronic Obstructive Pulmonary Disease; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: MedDRA PTs with frequency ≥3 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 event.

The frequency distribution of the 92 relevant medical history PTs defining frail patients with comorbidities reported in cases is presented in Table 67 below. A single case may contain more than 1 relevant medical history.

Table 67: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Medical History	Count of Medical History PTs During the Reporting Period[a,b]	Count of Medical History PTs Cumulatively[b]
Exercise lack of	66	103
Disability	9	28
Bedridden	7	10
Wheelchair user	5	11
Anorexia nervosa	2	4
Immobile	2	6
Walking aid user	1	8

Key: COPD=Chronic Obstructive Pulmonary Disease; PT=Preferred Term.

a: The medical history PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

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

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 58 cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were retrieved from Janssen Sponsored Clinical Studies. Of the 58 cases, 53 were from VAC31518COV3001 and 5 from VAC31518COV3009. Of all the events reported in these 58 cases, 11 were serious. Of these 58 cases, the most frequently reported country/territory of origin was Brazil (n=33). Of these 58 cases, 42 concerned males, 15 females, and 1 had no sex reported. The age range was from 24 to 75 years.

The events (≥2) included thrombocytopenia (n=38), platelet count decreased (n=6), deep vein thrombosis (n=3), and transient ischaemic attack (n=2). The mean and median TTO was 262.9 days and 316 days, respectively. Where reported (n=62), the outcomes were not resolved (n=24), resolving (n=21), and resolved (n=17). The Sponsor and Investigator's causality assessment of the events was reported as not related (n=57); and related (n=6). There was 1 case where the Sponsor assessed the causality as not related and the Investigator's causality was assessed as related (n=1).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting use in a frail patient with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) was retrieved from a Janssen Supported Clinical Study. This single case was from VAC31518COV4007. This case from [redacted] reported 3 nonserious events of injection site pain, pyrexia, and chills in a 59-year-old male. The TTO was on the same day as the first dose. The outcome for all the events was resolved. The Company and Sponsor's causality assessment was reported as related (n=3).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 32 cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 32 cases reported 102 serious EOI. Of these 32 cases, the most frequently reported country/territory of origin was the US (n=14) followed by Greece (n=6), and Germany (n=5). Of the 32 cases, 17 concerned males and 15 females. The age range was 21 to 96 years.

The events (n≥3) included expired product administered (n=5), pain in extremity (n=4), and confusional state, dizziness, dyspnoea, headache, and muscular weakness (n=3 each). The reported mean and median TTO was 122.8 days and 41 days, respectively. Where reported (n=83), the outcomes were not resolved (n=44), resolved (n=32), resolving (n=4), and fatal (n=3). The events with a fatal outcome were antiplatelet antibody positive, cerebral venous sinus thrombosis, and thrombocytopenia, which all occurred in a 48-year-old female with underlying anorexia nervosa who died due to CVST.

No ICSR literature cases were retrieved from the search strategy during the reporting period.

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 use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 8 (6 medically confirmed and 2 medically unconfirmed) cases were identified reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) who received the booster dose. There were 6 nonserious and 2 serious cases. All 8 cases were homologous. CIOMS II LL is presented in Appendix 7.13.

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database, no new safety information was identified for the missing information of use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders).

16.3.5.6. Interaction With Other Vaccines

Information on interaction with other vaccines has been presented in Section 15.3, Use With Concomitant Vaccination.

16.3.5.7. Long Term Safety

Introduction

According to the cRMP (version 3.0; dated 11 August 2021), long term safety is considered missing information for Ad26.COV2.S.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received cumulatively, reporting long-term safety. For the purposes of this review, long term safety is defined as cases with a latency of ≥6 months after the primary vaccination.

Results/Discussion

Cumulatively, 260 (112 medically confirmed and 148 medically unconfirmed) cases with a latency of ≥6 months were identified. Of these cases, 99 cases were serious and 161 nonserious, and reported a total of 534 events (132 serious; 402 nonserious).

Of these 260 cumulative cases received, 47 were reported from Janssen Sponsored Clinical Studies, 41 from Janssen Supported Clinical Studies, and 172 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 68 below.

Table 68: Characteristics of Cumulative Cases Involving the Use of Ad26.COV2.S and Reporting Long Term Safety

Case Characteristics		Number of Cases Received Cumulatively=260
Sex	Female	123
	Male	96
	NR	41
Age (Years)	0 to 17	1
Minimum: 17	18 to 35	32
Maximum: 95	36 to 50	35
Mean: 50.5	51 to 64	44
Median: 51.5	≥65	32
	Adult	4
	NR	112
Source	Spontaneous	164
	Clinical study (interventional; non-solicited)	87
	Clinical study (non-interventional; solicited)	8

Table 68: Characteristics of Cumulative Cases Involving the Use of Ad26.COV2.S and Reporting Long Term Safety

Case Characteristics		Number of Cases Received Cumulatively=260
	Clinical study (non-interventional; non-solicited)	1
Country/Territory	United States	142
	South Africa	52
	Brazil	13
	Croatia	13
	Czech Republic	6
	Germany	5
	Spain	5
	Argentina	4
	Philippines	4
	Colombia	3
	Portugal	3
	Italy	2
	Norway	2
	Belgium	1
	Iceland	1
	Lithuania	1
	Netherlands	1
	Poland	1
	Puerto Rico	1
Event Characteristics		**Number of Events=534**
Seriousness (Event Level)[a]	Nonserious	402
	Serious	132
Outcome (Event Level)[a]	Resolved	135
	Resolving	71
	Not resolved	65
	Fatal	12
	Resolved with sequelae	2
	NR	249

Key: NR=Not Reported.
a: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

The frequency distribution of the MedDRA PTs reported in cumulative cases reporting long term safety with the use of Ad26.COV2.S is presented in Table 69 below. A single case may contain more than 1 event.

Table 69: Frequency of MedDRA PTs in Cumulative Cases Reporting Long Term Safety With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported Cumulatively[a]	
	Serious	Nonserious
COVID-19	39	6
Pyrexia	3	38
Headache	2	29
Chills	0	24
Pain	0	22
Fatigue	0	17
Thrombocytopenia	1	15
Off label use	0	11
Pain in extremity	1	10

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

a: The MedDRA PTs with frequency >10 were sorted by decreasing order. A single case may contain more than 1 event.

Janssen Sponsored Clinical Studies

Cumulatively, 47 cases with a latency of ≥6 months were retrieved from Janssen Sponsored Clinical Studies. Forty-five cases were from VAC31518COV3001, and 1 each from VAC31518COV1001 and VAC31518COV3009. These 47 cases reported a total of 49 events (23 serious; 26 nonserious). Of these 47 cases, the most frequently reported country/territory of origin was the US (n=16), followed by Brazil and South Africa (n=12 each). Of these 47 cases, 26 concerned males and 21 females. The age range was from 27 to 80 years.

The events (n≥5) included thrombocytopenia (n=16) and exposure during pregnancy (n=5). The mean and median TTO was 292.6 days and 302 days, respectively. Where reported (n=42), the outcomes were resolved (n=16), resolving (n=14), and not resolved (n=12). The Sponsor's causality assessment of the events was reported as not related (n=47) and related (n=2), and the Investigator's causality assessment of the events was reported as not related (n=46), related (n=2), and not reported (n=1).

Janssen Supported Clinical Studies

Cumulatively, 41 cases with a latency of ≥6 months were retrieved from Janssen Supported Clinical Studies. Thirty-three cases were from VAC31518COV3021, 7 from VAC31518COV3012, and 1 from VAC31518COV4007. These 41 cases reported a total of 43 events (40 serious; 3 nonserious). Of these 41 cases, the most frequently reported country/territory of origin was South Africa (n=40) followed by Brazil (n=1). Of these 41 cases, 35 concerned females and 6 males. The age range was from 26 to 76 years.

The events (≥37) included COVID-19 (n=37). The mean and median TTO was 251.8 days and 270 days, respectively. Where reported (n=42), the outcomes were resolved (n=33), fatal (n=7), and resolving (n=2). The Company's causality assessment of the events was reported as not related (n=39), and related (n=4), and the Sponsor's causality assessment of the events was

reported as not related (n=38), related (n=4), and not reported (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

Cumulatively, 172 cases with a latency of ≥6 months were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 172 cases reported 69 serious EOI. Of these 172 cases, the most frequently reported country/territory of origin was the US (n=126) followed by Croatia (n=13). Of the 172 cases, 67 cases concerned females, 64 males, and 41 had no sex reported. The age range was from 17 to 95 years.

The events (n>20) included pyrexia (n=40), headache (n=30), chills (n=23), and pain (n=22). The reported mean and median TTO was 95.1 days and 0 days, respectively. Where reported (n=201), the outcomes were resolved (n=86), resolving (n=55), not resolved (n=53), fatal (n=5), and resolved with sequelae (n=2). The events reported with a fatal outcome were death (n=3), and intracardiac thrombus and thrombosis (n=1 each).

No ICSR literature cases were retrieved from the search strategy during the cumulative period.

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 the missing information of long term safety being causally associated with Ad26.COV2.S.

Conclusion

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

16.3.6. Adverse Events of Special Interest

As a part of its comprehensive routine pharmacovigilance activities to monitor safety of the Ad26.COV2.S vaccine use under US FDA EUA and EMA conditional marketing authorisation (cMA), the MAH has initiated sequential inferential analyses to support and complement ongoing safety surveillance activities through retrospective analysis of observational claims data available in the HealthVerity marketplace (HealthVerity 2021). The objective of these analyses, referred to as real-world data (RWD) analyses is to assess the potential association between the occurrence of predefined Adverse Events of Special Interest (AESI)s and vaccination with the Ad26.COV2.S. The current analysis includes (1) Pulmonary Embolism (PE), (2) DVT, (3) ischemic (non-haemorrhagic) stroke, (4) haemorrhagic stroke, (5) acute myocardial infarction, (6) thrombocytopenia and (7) immune thrombocytopenia, as well as associated composite outcomes, ie, composite venous thromboembolism (DVT OR PE), and composite stroke (ischemic OR haemorrhagic stroke). Ad26.COV2.S was analysed with self-controlled case series (SCCS) designs to quantify risk relative to unexposed time. A comparative cohort design was applied to

compare the risk of each outcome following exposure to Ad26.COV2.S vs. mRNA vaccine exposure. Specifications and results of these analysis are presented in Appendix 13. Key results of these analysis are covered by the analysis.

16.3.6.1. Cardiac Disorders

16.3.6.1.1. Arrhythmia

Introduction

Arrhythmia is listed as an AESI in the cRMP, European Risk Management Plan (EU RMP), and the United States Pharmacovigilance Plan (US PVP).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60 years old. Observed counts included EOI originating from valid initial and booster Individual Case Safety Reports (ICSR) that occurred within the risk window (Day: 1 to 14) and where TTO was day 0 or not reported. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 370 (117 medically confirmed and 253 medically unconfirmed) cases reporting arrhythmia were identified. Of these cases, 347 were serious and 23 nonserious, and reported a total of 421 events (369 serious; 52 nonserious).

Of these 370 cases during the reporting period of 25 August 2021 to 24 February 2022, 30 were reported from Janssen Sponsored Clinical Studies, and 340 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 597 (208 medically confirmed and 389 medically unconfirmed) cases reporting arrhythmia were identified. Of these cases, 534 were serious and 63 nonserious, and reported a total of 669 events (555 serious; 114 nonserious).

Of these 597 cumulative cases received, 50 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 546 from Post-marketing Sources

(including spontaneous and solicited cases).

An overview of these cases is presented in Table 70 below.

Table 70: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Arrhythmia

Case Characteristics		Number of Cases Received During the Reporting Period=370	Number of Cases Received Cumulatively=597
Sex	Male	198	298
	Female	163	281
	NR	9	18
Age (Years)[a]	18 to 35	78	104
Minimum: 19	36 to 50	90	137
Maximum: 98	51 to 64	94	165
Mean: 51.2	≥65	85	147
Median: 52	Adult	6	9
	Elderly	0	1
	NR	17	34
Source	Spontaneous	336	540
	Clinical study (interventional; non-solicited)	30	51
	Clinical study (non-interventional; solicited)	4	6
Country/Territory[b]	Germany	137	146
	United States	117	256
	France	16	22
	Netherlands	14	36
	Belgium	8	11
	Lithuania	8	12
	Spain	7	8
	Brazil	6	10
	Romania	6	6
	Austria	5	5
	Italy	5	11
	South Africa	5	8
	Colombia	4	6
	Argentina	3	3
	Czech Republic	3	3
	Estonia	3	4
	Hungary	3	3
	Iceland	3	9
	Ireland	3	4
	United Kingdom	3	4
	Croatia	2	3
	Latvia	2	3

Table 70: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Arrhythmia

Case Characteristics		Number of Cases Received During the Reporting Period=370	Number of Cases Received Cumulatively=597
Event Characteristics		**Number of Events=421**	**Number of Events=669**
Seriousness (Event Level)[c]	Serious	369	555
	Nonserious	52	114
Outcome (Event Level)[c]	Not resolved	159	233
	Resolved	101	174
	Resolving	48	78
	Fatal	21	35
	Resolved with sequelae	17	22
	NR	75	127

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting arrhythmia with the use of Ad26.COV2.S is presented in Table 71 below. A single case may contain more than 1 EOI.

Table 71: Frequency of MedDRA PTs in Cases Reporting Arrhythmia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	**Nonserious**	**Serious**	**Nonserious**
Arrhythmia	178	0	226	0
Atrial fibrillation	81	0	150	1
Heart rate irregular	11	20	17	55
Extrasystoles	12	5	13	16
Sinus tachycardia	9	5	14	10
Supraventricular tachycardia	7	6	12	6
Ventricular extrasystoles	6	5	9	13
Atrial flutter	9	1	13	2
Cardiac flutter	8	0	14	0
Pulseless electrical activity	6	0	12	0
Ventricular fibrillation	6	0	12	0
Atrioventricular block	5	0	8	0
Bundle branch block right	4	1	8	1

Table 71: Frequency of MedDRA PTs in Cases Reporting Arrhythmia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sinus bradycardia	4	1	4	1
Atrioventricular block first degree	3	0	4	0
Bundle branch block left	2	1	3	1
Supraventricular extrasystoles	2	1	3	2
Atrioventricular block second degree	1	1	3	1
Electrocardiogram repolarisation abnormality	2	0	3	0
Sinus arrhythmia	1	1	1	1
Tachyarrhythmia	1	1	1	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest with frequency ≥2 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 30 cases reporting arrhythmia were retrieved from Janssen Sponsored Clinical Studies. Of the 30 cases, 16 were from VAC31518COV3001, 13 were from VAC31518COV3009, and 1 from VAC31518COV2008. These 30 cases reported 33 serious EOI. Of these 30 cases, the most frequently reported country/territory of origin was the US (n=12). Of these 30 cases, 23 concerned males and 7 females. The age range was 35 to 87 years.

The EOI (≥2) included atrial fibrillation (n=16), supraventricular tachycardia (n=3), and arrhythmia, atrial flutter, atrioventricular block, sinus bradycardia (n=2 each). The mean and median TTO was 270.6 days and 280 days, respectively. The outcome of the 33 EOI were reported as resolved (n=16), resolving (n=7), not resolved (n=6), and resolved with sequelae (n=4). No fatal events occurred during the reporting period. The Sponsor and Investigator's causality assessment was reported as not related in all cases (n=33).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 340 cases reporting arrhythmia were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 340 cases reported 336 serious EOI. Of these 340 cases, the most frequently reported country/territory of origin was Germany (n=137) followed by the US (n=105), and France (n=16). Of the 340 cases, 175 concerned males, 156 females, and 9 had no sex reported. The age range was 19 to 98 years.

The EOI (n≥8) included arrhythmia (n=176), atrial fibrillation (n=65), heart rate irregular (n=30), extrasystoles (n=16), sinus tachycardia (n=14), ventricular extrasystoles (n=11), supraventricular tachycardia (n=10), and atrial flutter and cardiac flutter (n=8 each). The reported mean and median TTO was 39.6 days and 3 days, respectively. Where reported (n=313), the outcomes were not resolved (n=153), resolved (n=85), resolving (n=41), fatal (n=21), and resolved with sequelae (n=13). The events with a fatal outcome were atrial fibrillation (n=8), pulseless electrical activity (n=4), arrhythmia (n=2), and atrial flutter, atrioventricular block first degree, bundle branch block right, sinus arrest, supraventricular tachycardia, ventricular fibrillation, and ventricular tachycardia (n=1 each).

No ICSR literature cases were retrieved from the search strategy during the reporting period.

Fatal Cases

A total of 18 cases reported fatal outcomes (see Appendix 7.14.1). Of these 18 cases, 12 reported TTO outside of the risk window of 14 days. Eleven cases are medically confirmed, and 1 is medically unconfirmed. Patients' age ranged from 30 to 94 years, 5 were male, and the TTO ranged from 18 to 293 days post-vaccination. The cause of death was reported due to cardiac causes, pneumonia and sepsis (n=1), COVID-19 (n=1), COVID-19, cardiac causes and embolism (n=3 each), cardiac causes and pulmonary embolism (n=1), disseminated intravascular coagulation (n=1), renal impairment, cardiac causes, COVID-19, gastrointestinal hemorrhage (n=1), and unspecified cause (n=4). Eleven cases reported an alternative aetiology/identified risk factor for the development of an EOI. The alternative aetiologies/risk factors included concurrent COVID-19 (n=9), underlying cardiac history and osteomyelitis (n=1 each). The remaining case lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Of these 12 cases, 1 reported the age of the patient as ≤40 years. In this case, a 30-year old male with a risk factor of obesity (height and weight details not reported) experienced dyspnoea in the same month of vaccination with Ad26.COV2.S. On Day 55 post-vaccination, the patient was hospitalised after a syncopal episode. The patient had acute right coronary artery thrombosis and underwent percutaneous coronary intervention and thrombectomy. The patient was noted to have cardiomyopathy with an EF of less than 20%. Several hours later while in the intensive care unit (ICU), the patient experienced seizures followed by pulseless electrical activity arrest presumed

pulmonary embolism. The patient died from cardiomyopathy, coronary artery thrombosis, pulmonary embolism, pulseless electrical activity, seizure, syncope, PO_2 decreased, and ejection fraction decreased. In addition to the long latency and risk factor of obesity, further information on the result of the autopsy, the patient's complete medical history/concomitant medications, diagnostic workups are needed to confirm the diagnoses and to exclude other causes.

Six cases reported TTO within the risk window of 14 days. Three cases are medically confirmed, and 3 are medically unconfirmed. Three patients are male, age was reported in 5 cases and ranged from 49 to 73 years, and TTO was reported in 4 and ranged from 0 to 7 days post-vaccination. The cause of death was reported due to cardiac causes (n=3), shock (n=1), pulmonary embolism (n=1) and unspecified causes (n=1). The majority of the cases (5/6, 83.3%) reported an alternative aetiology/identified risk factor for the development of an EOI. The alternative aetiologies/risk factors included myocardial infarction (n=2), biventricular dilatation (n=1), aortic valve incompetence (n=1) and lung cancer (n=1). One case lacked essential information (medical history/concurrent conditions, TTO, concomitant medications) precluding any meaningful medical assessment.

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 arrhythmia being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 18 (6 medically confirmed and 12 medically unconfirmed) cases were identified reporting arrhythmia in individuals who received the booster dose. There were 16 serious and 2 nonserious cases. Of these cases, 9 were heterologous and 9 were homologous. CIOMS II LL is presented in Appendix 7.14.2.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis for arrythmia are presented in Table 72.

Table 72: Arrhythmia: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	83.27	0.080	(0.064, 0.100)	0.161	(0.128, 0.199)
	≥60	67.44	0.023	(0.018, 0.029)	0.046	(0.035, 0.058)
EU	18 to 59	201.79	0.091	(0.079, 0.105)	0.190	(0.165, 0.218)
	≥60	47.12	0.015	(0.011, 0.020)	0.030	(0.022, 0.040)

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

a: Counts included EOI (from valid/invalid cases) that occurred within the risk window (day: 1 to 14) and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis was not required.

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

Conclusion

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

Since launch, no signal for arrythmias overall nor single phenotypes has been observed for Ad26.COV2.S. Based on this, the Company proposes to monitor these cases through routine pharmacovigilance activities.

16.3.6.1.2. Cardiac Inflammatory Disorders, Including Myocarditis and Pericarditis

Introduction

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

On 17 October 2021, the Company received feedback from the US Center for Biologics Evaluation and Research (CBER) related to the Emergency Use Authorisation (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.

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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 29, 3039, 40 to 49, 50 to 64, 65 to 74 and ≥75. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window

(day: 1 to 42) and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 222 (102 medically confirmed and 120 medically unconfirmed) cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis were identified. All 222 cases were serious and reported a total of 234 serious events.

All 222 cases were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 365 (208 medically confirmed and 157 medically unconfirmed) cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis were identified. All 365 cases were serious and reported a total of 386 serious events.

Of these 365 cumulative cases received, 3 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 360 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 73 below.

Table 73: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Period=222	Number of Cases Received Cumulatively=365
Sex	Male	147	235
	Female	62	108
	NR	13	22
Age (Years)[a]	18 to 35	94	159
Minimum: 18	36 to 50	44	74
Maximum: 95	51 to 64	49	72
Mean: 40.2	≥65	14	29
Median: 37	Adult	1	2
	NR	20	29
Source	Spontaneous	221	359
	Clinical study (non-interventional; solicited)	1	1

Table 73: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Period=222	Number of Cases Received Cumulatively=365
	Clinical study (interventional; non-solicited)	0	5
Country/Territory[b]	United States	96	182
	Germany	48	62
	Netherlands	18	28
	Italy	14	15
	Austria	7	9
	France	7	10
	Greece	4	5
	Romania	4	4
	Czech Republic	3	3
	Denmark	3	8
	Portugal	3	4
	Canada	2	2
	Ireland	2	5
	Latvia	2	2
	Switzerland	2	2
	Belgium	1	7
	Colombia	1	1
	Egypt	1	1
	Iceland	1	1
	Korea, Republic of	1	1
	Lithuania	1	1
	Luxembourg	1	1
Event Characteristics		**Number of Events=234**	**Number of Events=386**
Seriousness (Event Level)[c]	Serious	234	386
Outcome (Event Level)[c]	Not resolved	92	135
	Resolved	33	58
	Resolving	29	52
	Resolved with sequelae	6	6
	Fatal	5	13
	NR	69	122

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis with the use of Ad26.COV2.S is presented in Table 74 below. A single case may contain more than 1 EOI.

Table 74: Frequency of MedDRA PTs in Cases Reporting Cardiac Inflammatory Disorders, Including Myocarditis and Pericarditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	132	0	201	0
Pericarditis	99	0	179	0
Pleuropericarditis	2	0	3	0
Eosinophilic myocarditis	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 222 cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 222 cases reported 234 serious EOI. Of these 222 cases, the most frequently reported country/territory of origin was the US (n=96) followed by Germany (n=48), and the Netherlands (n=18). Of the 222 cases, 147 concerned males, 62 females, and 13 had no sex reported. The age range was 18 to 95 years.

The EOI included myocarditis (n=132), pericarditis (n=99), pleuropericarditis (n=2), and eosinophilic myocarditis (n=1). The reported mean and median TTO was 41.6 days and 14 days, respectively. Where reported (n=165), the outcomes were not resolved (n=92), resolved (n=33), resolving (n=29), resolved with sequelae (n=6), and fatal (n=5). The events with a fatal outcome were myocarditis (n=3), and eosinophilic myocarditis and pericarditis (n=1 each).

Four ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the

currently known information on cardiac inflammatory disorders, including myocarditis and pericarditis.

Fatal Cases

A total of 6 fatal cases were received during the reporting period, of which 5 had a fatal outcome, and for a 1, the outcome was not reported. Of these 6 cases, 2 reported a TTO outside of the risk window of 42 days, and both were medically confirmed. The first case concerned a 51-year-old female who experienced and died from eosinophilic myocarditis on day 96 post-vaccination with Ad26.COV2.S. This case lacks essential information regarding the patient's medical history, concomitant medication, the clinical course of events, and diagnostic and laboratory results precluding any meaningful medical assessment. The second case concerned a 69-year-old male who experienced myocarditis 89 days post-vaccination with Ad26.COV2.S. The patient died 91 days post-vaccination from myocarditis This case reported an alternative aetiology/identified risk factor as virial infection (not specified) for the development of an EOI and lacks essential information regarding the patient's medical history, the clinical course of events, and laboratory results precluding any meaningful medical assessment.

Four cases reported TTO within the risk window of 42 days. Three cases were medically confirmed, and the remaining case was not medically confirmed. The first case concerned a 67-year-old female who experienced myocarditis on the same day after vaccination with Ad26.COV2.S. The patient died 39 days post-vaccination (cause of death was not reported). This case lacks essential information regarding the patient's medical history, the clinical course of events, autopsy, and diagnostic and laboratory results precluding any meaningful medical assessment. The second case concerned a 62-year-old female who experienced myocarditis on an unspecified day after vaccination with Ad26.COV2.S. The patient died on an unspecified day post-vaccination from cardiac arrest and myocarditis. This case reported an alternative aetiology/identified risk factor as melanoma for the development of an EOI and lacks essential information regarding the clinical course of events and TTO precluding any meaningful medical assessment. The third case concerned a 55-year-old female who experienced myocarditis 6 days post-vaccination with Ad26.COV2.S. The patient died 140 days post-vaccination from myocarditis. This case lacks essential information regarding the patient's medical history, the clinical course of events, autopsy, and diagnostic and laboratory results precluding any meaningful medical assessment. The fourth case concerned female (age unspecified) who experienced myocarditis on an unspecified day after vaccination with Ad26.COV2.S. The patient died on an unspecified day post-vaccination (cause of death was not reported). This case lacks essential information regarding the patient's medical history, the clinical course of events, autopsy, and diagnostic and laboratory results precluding any meaningful medical assessment.

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 cardiac inflammatory disorders, including myocarditis and pericarditis being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 4 serious (1 medically confirmed and 3 medically unconfirmed) cases were identified reporting cardiac inflammatory disorders, including myocarditis and pericarditis in individuals who received the booster dose. Of these cases, 2 were heterologous and 2 were homologous. CIOMS II LL is presented in Appendix 7.15.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis for myocarditis are presented in Table 75.

Table 75: Myocarditis: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

		Broad 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	5.08	2.991	(0.982, 6.936)	21.732	(7.137, 50.397)
		30 to 39	7.54	2.437	(1.020, 4.895)	10.886	(4.557, 21.871)
		40 to 49	6.66	2.010	(0.786, 4.214)	7.998	(3.126, 16.767)
		50 to 64	8.36	1.751	(0.773, 3.402)	7.398	(3.265, 14.372)
		65 to 74	5.43	1.034	(0.355, 2.336)	3.639	(1.251, 8.222)
		≥75	0.74	0.295	(0.002, 2.037)	1.141	(0.009, 7.887)
	Male	18 to 29	15.66	1.211	(0.687, 1.976)	3.926	(2.229, 6.409)
		30 to 39	9.70	1.157	(0.547, 2.147)	3.781	(1.789, 7.017)
		40 to 49	6.86	1.331	(0.529, 2.762)	4.588	(1.824, 9.520)
		50 to 64	5.81	0.647	(0.233, 1.425)	2.362	(0.849, 5.204)
		65 to 74	1.70	0.418	(0.038, 1.657)	1.598	(0.147, 6.338)
		≥75	0.32	0.142	(0.000, 1.926)	0.585	(0.000, 7.926)
EU	Female	18 to 29	4.93	2.784	(0.895, 6.534)	20.230	(6.502, 47.477)
		30 to 39	2.67	0.743	(0.134, 2.300)	3.318	(0.599, 10.274)
		40 to 49	6.68	1.683	(0.659, 3.524)	6.696	(2.621, 14.022)
		50 to 64	4.90	0.982	(0.314, 2.311)	4.150	(1.328, 9.762)
		65 to 74	1.10	0.237	(0.008, 1.240)	0.836	(0.028, 4.364)
		≥75	0.04	0.017	(0.000, 1.587)	0.065	(0.000, 6.145)
	Male	18 to 29	33.14	2.418	(1.666, 3.393)	7.841	(5.402, 11.003)
		30 to 39	14.80	1.529	(0.852, 2.530)	4.997	(2.784, 8.270)
		40 to 49	6.69	1.081	(0.423, 2.262)	3.725	(1.460, 7.798)
		50 to 64	10.85	1.168	(0.580, 2.098)	4.264	(2.117, 7.659)
		65 to 74	2.13	0.614	(0.082, 2.142)	2.349	(0.313, 8.193)
		≥75	1.04	0.548	(0.016, 2.972)	2.255	(0.064, 12.232)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42) and where time-to-onset was day 0 or not reported.

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

A review of the myocarditis results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of >1 for all female age groups and males: 18 to 29, 30 to 39, 40 to 49 age groups. In the EU, an O/E ratio

of >1 was observed for females: 18 to 29 and 40 to 49 age groups and males: 18 to 29, 30 to 39, 40 to 49 and 50 to 64 age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 for all female age groups and all male age groups except the ≥75 age group. In the EU, the sensitivity analysis O/E ratio was >1 for females: 18 to 29, 30 to 39, 40 to 49, 50 to 64 age groups and all male age groups.

A restricted O/E analysis with sensitivity analysis was performed for myocarditis. This included EOI that were known to have occurred within the risk window (day: 1 to 42) only.

Results of the restricted O/E and sensitivity analysis for myocarditis are presented in Table 76.

Table 76: Myocarditis: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	Female	18 to 29	4.00	2.355	(0.642, 6.030)	17.112	(4.662, 43.813)
		30 to 39	4.00	1.293	(0.352, 3.310)	5.775	(1.573, 14.786)
		40 to 49	3.00	0.905	(0.187, 2.646)	3.603	(0.743, 10.528)
		50 to 64	4.00	0.838	(0.228, 2.145)	3.540	(0.964, 9.063)
		65 to 74	3.00	0.571	(0.118, 1.669)	2.010	(0.415, 5.875)
		≥75	0.00	0.000	(0.000, 1.470)	0.000	(0.000, 5.690)
	Male	18 to 29	13.00	1.005	(0.535, 1.719)	3.259	(1.736, 5.574)
		30 to 39	4.00	0.477	(0.130, 1.221)	1.559	(0.425, 3.992)
		40 to 49	5.00	0.970	(0.315, 2.264)	3.344	(1.086, 7.804)
		50 to 64	3.00	0.334	(0.069, 0.977)	1.220	(0.252, 3.565)
		65 to 74	1.00	0.246	(0.006, 1.369)	0.940	(0.024, 5.237)
EU	Female	18 to 29	3.00	1.694	(0.349, 4.951)	12.311	(2.539, 35.977)
		30 to 39	1.00	0.278	(0.007, 1.550)	1.243	(0.031, 6.924)
		40 to 49	6.00	1.511	(0.555, 3.290)	6.014	(2.207, 13.090)
		50 to 64	3.00	0.601	(0.124, 1.757)	2.541	(0.524, 7.425)
	Male	18 to 29	27.00	1.970	(1.298, 2.866)	6.388	(4.210, 9.294)
		30 to 39	12.00	1.240	(0.641, 2.165)	4.052	(2.094, 7.078)
		40 to 49	3.00	0.485	(0.100, 1.416)	1.671	(0.345, 4.882)
		50 to 64	9.00	0.969	(0.443, 1.839)	3.537	(1.617, 6.714)
		65 to 74	2.00	0.577	(0.070, 2.083)	2.205	(0.267, 7.966)
		≥75	1.00	0.527	(0.013, 2.936)	2.168	(0.055, 12.082)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42) only.

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

A review of the myocarditis results for the US and EU restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of >1 for females: 18 to 29, 30 to 39 age groups and males: 18 to 29 age group. In the EU, an O/E ratio of >1 was observed for females: 18 to 29 and 40 to 49 age groups, and males: 18 to 29

and 30 to 39 age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 for all female age groups except the ≥75 age group and all male age groups except the 65 to 74 age group. In the EU, the sensitivity analysis showed an O/E ratio of >1 for all the male and female age groups.

Results of the broad O/E and sensitivity analysis for pericarditis are presented in Table 77.

Table 77: Pericarditis: Broad O/E and Sensitivity Analysis results (Cumulative to 24 February 2022)

Broad 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	5.65	0.349	(0.123, 0.778)	1.050	(0.371, 2.337)
		30 to 39	7.92	0.373	(0.160, 0.738)	0.994	(0.427, 1.964)
		40 to 49	1.99	0.115	(0.014, 0.416)	0.306	(0.037, 1.108)
		50 to 64	12.01	0.272	(0.141, 0.475)	0.709	(0.366, 1.238)
		65 to 74	3.85	0.182	(0.048, 0.473)	0.483	(0.127, 1.259)
		≥75	1.44	0.161	(0.011, 0.707)	0.453	(0.030, 1.988)
	Male	18 to 29	18.53	0.243	(0.145, 0.382)	0.588	(0.351, 0.923)
		30 to 39	13.56	0.215	(0.116, 0.364)	0.508	(0.274, 0.859)
		40 to 49	9.69	0.225	(0.106, 0.417)	0.536	(0.253, 0.994)
		50 to 64	5.45	0.074	(0.026, 0.168)	0.183	(0.063, 0.412)
		65 to 74	5.56	0.164	(0.057, 0.368)	0.413	(0.144, 0.924)
		≥75	0.26	0.019	(0.000, 0.309)	0.051	(0.000, 0.820)
EU	Female	18 to 29	3.65	0.217	(0.054, 0.577)	0.651	(0.163, 1.735)
		30 to 39	0.47	0.019	(0.000, 0.187)	0.051	(0.000, 0.499)
		40 to 49	1.48	0.071	(0.005, 0.308)	0.190	(0.013, 0.819)
		50 to 64	8.21	0.178	(0.078, 0.348)	0.464	(0.203, 0.906)
		65 to 74	0.07	0.004	(0.000, 0.205)	0.010	(0.000, 0.546)
		≥75	1.03	0.122	(0.003, 0.664)	0.342	(0.009, 1.869)
	Male	18 to 29	15.14	0.187	(0.105, 0.308)	0.453	(0.254, 0.746)
		30 to 39	7.80	0.107	(0.046, 0.213)	0.253	(0.108, 0.503)
		40 to 49	3.69	0.071	(0.018, 0.189)	0.170	(0.043, 0.451)
		50 to 64	14.27	0.188	(0.104, 0.314)	0.462	(0.254, 0.772)
		65 to 74	0.13	0.005	(0.000, 0.137)	0.011	(0.000, 0.344)
		≥75	0.04	0.003	(0.000, 0.328)	0.009	(0.000, 0.870)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42) and where time-to-onset was day 0 or not reported.

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

A review of the pericarditis results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incidence rate) showed for the US and EU an O/E ratio of <1 for both males and females across all age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 for females: 18 to 29 age group only. In the EU, the sensitivity analysis O/E ratio was <1 for all male and female age groups.

A restricted O/E analysis with sensitivity analysis was performed for pericarditis. This included EOI that were known to have occurred within the risk window (day: 1 to 42) only.

Results of the restricted O/E and sensitivity analysis for pericarditis are presented in Table 78.

Table 78: Pericarditis: Restricted O/E and Sensitivity Analysis results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	Female	18 to 29	5.00	0.309	(0.100, 0.722)	0.929	(0.302, 2.168)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42) only.
b: Poisson exact confidence interval (95% CI).

A review of the pericarditis restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) and sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) results showed an O/E ratio of <1 for the US female: 18 to 29 age group.

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

Conclusion

On 17 October 2021, the Company received feedback from the US Center for Biologics Evaluation and Research (CBER) related to the Emergency Use Authorisation (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.

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 both for the reporting period and cumulative, and an O/E analysis, no new critical safety information was identified during the reporting period for cardiac inflammatory disorders, including myocarditis and pericarditis. The Company will continue to closely monitor cardiac inflammatory disorders as an AESI.

16.3.6.1.3. 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 30) and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 29 (18 medically confirmed and 11 medically unconfirmed) cases reporting cardiomyopathy were identified. All 29 cases were serious and reported a total of 32 events (30 serious; 2 nonserious).

Of these 29 cases during the reporting period of 25 August 2021 to 24 February 2022, 2 were reported from Janssen Sponsored Clinical Studies and 27 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 55 (37 medically confirmed and 18 medically unconfirmed) cases reporting cardiomyopathy were identified. All 55 cases were serious and reported a total of 62 events (59 serious; 3 nonserious).

Of these 55 cumulative cases received, 2 were reported from Janssen Sponsored Clinical Studies, and 53 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

An overview of these cases is presented in Table 79 below.

Table 79: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cardiomyopathy

Case Characteristics		Number of Cases Received During the Reporting Period=29	Number of Cases Received Cumulatively=55
Sex	Male	17	35
	Female	9	17
	NR	3	3
Age (Years)[a]	18 to 35	1	7
Minimum: 30	36 to 50	6	12
Maximum: 82	51 to 64	11	20
Mean: 59.6	≥65	9	14
Median: 60	NR	2	2
Source	Spontaneous	27	53
	Clinical study (interventional; non-solicited)	2	2
Country/Territory[b]	United States	18	40
	Germany	5	7
	France	2	2
	Argentina	1	1
	Canada	1	1
	Czech Republic	1	1
	Netherlands	1	1
Event Characteristics		**Number of Events=32**	**Number of Events=62**
Seriousness (Event Level)[c]	Serious	30	59
	Nonserious	2	3
Outcome (Event Level)[c]	Not resolved	13	22
	Fatal	6	9
	Resolved	4	12
	Resolved with sequelae	1	1
	Resolving	1	4
	NR	7	14

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting cardiomyopathy with the use of Ad26.COV2.S is presented in Table 80 below. A single case may contain more than 1 EOI.

Table 80: Frequency of MedDRA PTs in Cases Reporting Cardiomyopathy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cardiomyopathy	8	0	17	0
Ejection fraction decreased	7	1	17	2
Stress cardiomyopathy	4	0	6	0
Congestive cardiomyopathy	3	0	6	0
Cardiomyopathy acute	2	0	2	0
Hypertrophic cardiomyopathy	2	0	2	0
Cardiac hypertrophy	0	1	1	1
Cardiac sarcoidosis	1	0	1	0
Eosinophilic myocarditis	1	0	1	0
Ischaemic cardiomyopathy	1	0	3	0
Myocardial fibrosis	1	0	3	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 EOI.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 2 cases reporting cardiomyopathy were retrieved from Janssen Sponsored Clinical Studies. Both cases were reported from VAC31518COV3001. These 2 cases reported 1 serious EOI each: a case of stress cardiomyopathy (n=1) in 73-year-old female from the [redacted] 112 days after receiving the first dose of Ad26.COV2.S, reported as resolved and not related by the Investigator; and a case of hypertrophic cardiomyopathy (n=1) in a 74-year-old female from [redacted] 370 days after receiving the first dose of Ad26.COV2.S, reported as resolved and not related by the Investigator.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 27 cases reporting events of cardiomyopathy were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 27 cases reported 25 serious EOI. Of these 27 cases, the most frequently reported country/territory of origin was the US (n=17) followed by Germany (n=5), and France (n=2). Of the 27 cases, 17 concerned males, 7 females, and 3 had no sex reported. The age range was 30 to 82 years.

The EOI (≥2) included cardiomyopathy, ejection fraction decreased (n=8 each), congestive cardiomyopathy, stress cardiomyopathy (n=3 each), and cardiomyopathy acute (n=2). The reported mean and median TTO was 102.5 days and 94 days, respectively. Where reported (n=23), the outcomes were not resolved (n=13), fatal (n=6), resolved (n=2), and resolved with sequelae and resolving (n=1 each). The events with a fatal outcome were ejection fraction decreased (n=3), cardiomyopathy (n=2), and eosinophilic myocarditis (n=1).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information on cardiomyopathy.

Fatal Cases

A total of 5 cases were received during the reporting period,4 of which reported a TTO outside of the risk window of 30 days.

All 4 cases occurring outside the risk window were medically confirmed. The patients' age ranged from 30 to 74 years, with 3 cases concerning females and 1 male, and the TTO ranged from 55 to 212 days post-vaccination. The cause of death was reported due to cardiac causes and COVID-19 infection (n=1), cardiac causes (n=2), unspecified cause (n=1). Two cases reported an alternative aetiology/identified risk factor for the development of an EOI. The alternative aetiologies/risk factors included myocardial infarction in a 73-year-old female who died of (acute MI, COVID-19 pneumonia, cardiomyopathy, hypercapnia, lung disorder, respiratory failure, respiratory tract haemorrhage, and respiratory tract inflammation) 216 days after vaccination and COVID-19 infection (n=1); and in a 74-year-old female whose cause of death was not reported, 195 days after vaccination (n=1). The remaining 2 cases lacked essential information (e.g. medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Of these 4 cases, 1 reported the age of the patient as ≤ 40 years. In this case, a 30-year-old male with a risk factor of obesity (height and weight details were not provided) experienced dyspnoea in the same month of vaccination with Ad26.COV2.S. On day 55 post-vaccination, the patient was hospitalised after a syncopal episode. The patient had acute right coronary artery thrombosis and underwent percutaneous coronary intervention and thrombectomy. The patient was noted to have cardiomyopathy with an ejection fraction (EF) of less than 20%. Several hours later while in the ICU, the patient experienced seizures followed by pulseless electrical activity arrest presumed pulmonary embolism. The patient died from cardiomyopathy, coronary artery thrombosis, pulmonary embolism, pulseless electrical activity, seizure, syncope, PO_2 decreased, and ejection fraction decreased. In addition to the long latency and risk factor of obesity, further information on the result of the autopsy, the patient's complete medical history/concomitant medications, diagnostic workups are needed to confirm the diagnoses and to exclude other causes.

The remaining case was medically confirmed and concerned 69-year-old male who died at home from coronary thrombosis with fresh myocardial infarction on day 9 post-vaccination with

Ad26.COV2.S. This case lacks essential information regarding the patient's medical history, concomitant medication, the clinical course of events, diagnostic and laboratory results precluding any meaningful medical assessment.

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

Booster Dose

Cumulatively, 2 (1 medically confirmed and 1 medically unconfirmed) cases were identified reporting cardiomyopathy in individuals who received the booster dose. Both cases were serious and heterologous. CIOMS II LL is presented in Appendix 7.16.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 81.

Table 81: Stress Cardiomyopathies: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	14.65	3.382	(1.878, 5.611)	6.942	(3.855, 11.516)
	≥60	8.34	0.670	(0.295, 1.302)	2.260	(0.996, 4.395)
EU	18 to 59	4.00	0.809	(0.220, 2.071)	1.660	(0.452, 4.251)
	≥60	5.00	0.481	(0.156, 1.122)	1.623	(0.527, 3.787)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 30) and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US 18 to 59 age group. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US and EU and O/E ratio of >1 in both age groups.

A restricted O/E analysis with sensitivity analysis. This included EOI that were known to have occurred within the risk window (day: 1 to 30) only. Results of the restricted O/E and sensitivity analysis are presented in Table 82.

Table 82: Stress Cardiomyopathies: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Restricted O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	12.00	2.770	(1.431, 4.839)	5.686	(2.938, 9.933)
	≥60	8.00	0.642	(0.277, 1.266)	2.168	(0.936, 4.272)
EU	18 to 59	2.00	0.404	(0.049, 1.461)	0.830	(0.101, 2.999)
	≥60	3.00	0.288	(0.059, 0.843)	0.974	(0.201, 2.845)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 30) only.
b: Poisson exact confidence interval (95% CI).

A review of the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of >1 in the 18 to 59 age group only. In the EU, the O/E ratio was <1 for both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 in both age groups. In the EU, the O/E ratio was <1 for both age groups.

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

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new critical safety information was identified during the reporting period for cardiomyopathy. The Company will continue to monitor cardiomyopathy as an AESI in upcoming periodic safety reports.

16.3.6.1.4. Coronary Artery Disease, Including Acute Myocardial Infarction

Introduction

Coronary artery disease, including acute myocardial infarction 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 28) and where TTO was

day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 406 (200 medically confirmed and 206 medically unconfirmed) cases reporting coronary artery disease, including acute myocardial infarction were identified. Of these cases, 404 were serious and 2 nonserious, and reported a total of 462 events (455 serious; 7 nonserious).

Of these 406 cases during the reporting period of 25 August 2021 to 24 February 2022, 73 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Studies, and 332 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 754 (434 medically confirmed and 320 medically unconfirmed) cases reporting coronary artery disease, including acute myocardial infarction were identified. Of these cases, 751 cases were serious and 3 nonserious, and reported a total of 917 events (907 serious; 10 nonserious).

Of these 754 cumulative cases received, 126 were reported from Janssen Sponsored Clinical Studies, 4 from Janssen Supported Clinical Study, and 624 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 83 below.

Table 83: Characteristics of 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 Reporting Period=406	Number of Cases Received Cumulatively=754
Sex	Male	246	467
	Female	137	250
	NR	23	37
Age (Years)[a]	18 to 35	48	80
Minimum: 18	36 to 50	83	131
Maximum: 97	51 to 64	123	249
Mean: 55.0	≥65	103	226
Median: 57	Adult	3	5
	Elderly	1	1
	NR	45	62

Table 83: Characteristics of 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 Reporting Period=406	Number of Cases Received Cumulatively=754
Source	Spontaneous	321	613
	Clinical study (interventional; non-solicited)	74	130
	Clinical study (non-interventional; solicited)	11	11
Country/Territory[b]	United States	214	454
	Germany	52	69
	Philippines	16	18
	South Africa	14	21
	France	13	24
	Italy	13	17
	Austria	11	13
	Belgium	8	20
	Brazil	8	11
	Romania	8	9
	Argentina	7	11
	Estonia	5	5
	Netherlands	5	21
	Colombia	4	12
	Poland	4	6
	Ireland	3	3
	Latvia	3	5
	Spain	3	10
	Iceland	2	3
	Portugal	2	3
Event Characteristics		**Number of Events=462**	**Number of Events=917**
Seriousness (Event Level)[c]	Serious	455	907
	Nonserious	7	10
Outcome (Event Level)[c]	Not resolved	121	211
	Resolved	105	238
	Fatal	67	141
	Resolving	45	79
	Resolved with sequelae	22	34
	NR	102	214

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to

Table 83: Characteristics of 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 Reporting Period=406	Number of Cases Received Cumulatively=754

24 February 2022).

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting coronary artery disease, including acute myocardial infarction with the use of Ad26.COV2.S is presented in Table 84 below. A single case may contain more than 1 EOI.

Table 84: Frequency of MedDRA PTs in Cases Reporting Coronary Artery Disease, Including Acute Myocardial Infarction With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocardial infarction	161	0	299	0
Angina pectoris	93	0	137	0
Acute myocardial infarction	80	0	164	0
Troponin increased	31	3	76	5
Coronary artery disease	19	1	39	2
Acute coronary syndrome	13	0	22	0
Coronary arterial stent insertion	9	0	28	0
Coronary artery occlusion	7	0	27	0
Coronary artery thrombosis	7	0	23	0
Myocardial ischaemia	7	0	14	0
Stress cardiomyopathy	4	0	6	0
Angina unstable	3	0	7	0
Coronary artery stenosis	3	0	9	0
Troponin I increased	3	0	9	0
Troponin T increased	1	2	1	2
Arteriosclerosis coronary artery	1	1	7	1
Coronary angioplasty	2	0	6	0
Coronary artery dissection	2	0	3	0
Percutaneous coronary intervention	2	0	7	0

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

Table 84: Frequency of MedDRA PTs in Cases Reporting Coronary Artery Disease, Including Acute Myocardial Infarction With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious

a: The MedDRA PTs of interest with frequency ≥2 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 73 cases reporting coronary artery disease, including acute myocardial infarction were retrieved from Janssen Sponsored Clinical Studies. Of the 73 cases, 45 were from VAC31518COV3001, 27 were from VAC31518COV3009, and 1 from VAC31518COV2008. These 73 cases reported 74 serious EOI. Of these 73 cases, the most frequently reported country/territory of origin was the US (n=32). Of these 73 cases, 59 concerned males and 14 females. The age range was 39 to 86 years.

The EOI (≥2) included acute myocardial infarction (n=26), myocardial infarction (n=20), coronary artery disease (n=8), myocardial ischaemia (n=5), acute coronary syndrome (n=4), angina pectoris (n=3), angina unstable and coronary artery stenosis (n=2 each). The mean and median TTO was 249.5 days and 279 days, respectively. The outcome of the 74 EOI were reported as resolved (n=56), fatal (n=7), resolving (n=5), not resolved (n=4), and resolved with sequelae (n=2). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=74).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting coronary artery disease, including acute myocardial infarction was retrieved from a Janssen Supported Clinical Study. This single case was from VAC31518COV3021. This case reported 1 serious EOI of myocardial infarction from [redacted], which concerned a 63-year-old female. The TTO was 255 days from the first dose. The outcome for this event was reported as resolving. EOI causality was reported as: Company assessed as not related and the Sponsor causality was not reported.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 332 cases reporting coronary artery disease, including acute myocardial infarction were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 332 cases reported 380 serious EOI. Of these 332 cases, the most frequently reported country/territory of origin was the US (n=182) followed by Germany (n=52), and France and Italy (n=13 each). Of the 332 cases, 187 concerned males, 122 females, and 23 had no sex reported. The age range was 18 to 97 years.

The EOI (n≥6) included myocardial infarction (n=140), angina pectoris (n=90), acute myocardial infarction (n=54), troponin increased (n=34), coronary artery disease (n=12), acute coronary syndrome (n=9), coronary arterial stent insertion (n=8), coronary artery thrombosis (n=7), and coronary artery occlusion (n=6). The reported mean and median TTO was 52.4 days and 12 days, respectively. Where reported (n=285), the outcomes were not resolved (n=117), fatal (n=60), resolved (n=49), resolving (n=39), and resolved with sequelae (n=20). The events with a fatal outcome were myocardial infarction (n=35), acute myocardial infarction (n=9), troponin increased (n=6), coronary artery disease and coronary artery thrombosis (n=3 each), coronary angioplasty, coronary ostial stenosis, myocardial ischaemia, and percutaneous coronary intervention (n=1 each).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed. There were 5 literature cases reported. In 1 case, the EOI were myocardial infarction (MI), coronary artery thrombosis, and arteriosclerosis coronary artery with a fatal progression. In addition to these EOI, cerebral venous thrombosis, heparin-induced thrombocytopenia test positive, and cardiac hypertrophy were also reported. The author considered the case to be Vaccine-induced Immune Thrombocytopenia (VITT), but no thrombocytopenia was reported. Despite the lack of complete clinical details including laboratory and diagnostics results, medical history, and cosuspect/concomitant medications, the causality of the vaccine cannot be excluded, considering the compatible TTO and the reported positive anti-PF4 (platelet factor) heparin antibody test. In the review of the remaining 4 cases, 1 concerned multiple patients, no information was identified that would change the characterisation of the risk.

Fatal Cases

During the reporting period, a total of 60 cases reported a fatal outcome. The event outcome was unknown/not reported in 10 cases. A line listing with the patient's main clinical details is provided in Appendix 7.17.1.

Of these 60 fatal cases, 3 cases were reported in multiple patients without identifiable details. Therefore, these cases are not discussed further. In addition, 7 cases were reported following a booster vaccine. These cases are discussed separately under the subsection below, "Fatal Booster Dose Cases."

Thirty-three cases reported a TTO within the risk window of 28 days. Thirteen cases were medically confirmed, and 20 were medically unconfirmed. Patient age was reported in 22 cases and ranged from 25 to 80 years, and TTO was reported in 21 cases and ranged from 0 to 27 days post-vaccination. The cause of death was reported due to cardiac causes (n=19), unspecified causes (n=11), multiple organ dysfunction syndrome and MI (n=1), shock (n=1), and obesity, hypertension, and diabetes (n=1). The majority of the cases (23/33, 70%) cases lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment. Eight cases reported an alternative aetiology/identified risk factor for the development

of an EOI. This included hypertension (n=4), underlying cardiac disorder (n=2), pulmonary embolism and COVID-19 infection, concurrent osteomyelitis, and possible opioid dependence (n=1 each). For the remaining 2 cases, 1 was received from literature, considering the short TTO for the EOI and in the absence of other risk factors, the causality of the vaccine could not be excluded.

Of these 33 cases, 2 reported the age of the patients as ≤ 40 years. Both cases lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, concomitant medications, and autopsy results precluding any meaningful medical assessment.

- In the first case, a 40-year-old male, who was reportedly fit and active, experienced a massive heart attack a week post-vaccination and died from an unknown cause.
- In the second case, a 25-year-old male died from a heart attack on an unspecified date post-vaccination.

Seventeen cases reported TTO outside of the risk window of 28 days. Thirteen cases were medically confirmed, and 4 were medically unconfirmed. Patient age was reported in 16 cases and ranged from 29 to 97 years and the TTO ranged from 30 to 293 days post-vaccination. The cause of death was reported due to cardiac causes (n=9), cardiac causes and COVID-19 infection (n=4), unspecified cause (n=2), and CVA, COVID-19 infection (n=1 each). Ten cases reported an alternative aetiology/identified risk factor for the development of an EOI. This included underlying cardiac history and COVID-19 infection (n=3), chronic kidney disease and COVID-19 infection, diabetes, hypertension, and COVID-19 infection (n=2 each), and risk factors of obesity, malignant neoplasm, recent surgery and family history of blood clots (n=1 each). Six cases lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment. In the remaining case, (reported in a 40-year-old patient, the case discussed below) the causality of the vaccine cannot be excluded, considering the reported age, health status, and temporal relationship; however, further information regarding detailed clinical course including diagnostic examinations and autopsy results were not provided for the case.

Of these 17 cases, 3 reported the age of the patients as ≤40 years. A summary of these 3 cases is shown below:

- In the first case, a 40-year-old male, who had no known allergies, had no history, and was healthy prior to injection complained of feeling very fatigued in the same month of vaccination and the patient died due to MI approximately 3 months post-vaccination. The death certificate indicated atherosclerotic cardiovascular disease as the immediate cause of death.
- In the second case, a 30-year-old male with a risk factor of obesity (height and weight details not provided) was hospitalised after a syncopal episode on day 55 post-vaccination. The patient had acute right coronary artery thrombosis and underwent percutaneous coronary intervention and thrombectomy. The patient was noted to have cardiomyopathy with an EF of less than 20%. Several hours later while in the ICU, the patient experienced seizures followed

by pulseless electrical activity arrest presumed pulmonary embolism. The patient died from cardiomyopathy, coronary artery thrombosis, pulmonary embolism, pulseless electrical activity, seizure, syncope, PO2 decreased, and ejection fraction decreased.

- In a third case, a 29-year-old male experienced acute MI, coronary ostial stenosis, cardiogenic shock, brain oedema, and hypoxic brain damage 105 days post-vaccination and was hospitalised. The next day, the patient died of cardiogenic shock.

Fatal Booster Dose Cases

Seven fatal cases occurred following a booster vaccination during the reporting interval.

Homologous Booster Dose

Three medically unconfirmed cases reported a fatal EOI following a booster with Ad26.COV2.S. In 2 cases, 1 reported death due to unspecified cause, and 1 reported death due to MI. TTO was not reported in 1 case and 1 reported TTO outside of the risk window of 28 days. Both cases lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, concomitant medications, and autopsy results) precluding any meaningful medical assessment. In the third case, received via social media, a 35-year-old female who was 100% healthy and never had any problems of any kind at the time of vaccination, died due to MI and thrombosis a week after receiving the booster dose. There were no reported EOI after the initial dose. "Autopsy confirmed it was from blood clots caused by the J&J vaccine". The causality of the vaccine cannot be excluded considering the close temporal relationship of events post-vaccination and in the absence of other risk factors.

Heterologous Booster Dose

Four cases involved a heterologous booster, where Ad26.COV2.S vaccine was reported as the primary dose and the booster dose was an mRNA vaccine. The TTO in relation to the primary dose was not reported, the EOI was reported in relation to the mRNA booster and it is unlikely that the event met the risk window of 28 days for the Ad26.COV2.S vaccine. The cause of death was MI in these 4 cases.

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 coronary artery disease, including acute myocardial infarction being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 17 serious (7 medically confirmed and 10 medically unconfirmed) cases were identified reporting coronary artery disease, including acute myocardial infarction in individuals who received the booster dose. Of these cases, 7 were heterologous and 10 were homologous CIOMS II LL is presented in Appendix 7.17.2.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 85.

Table 85: Coronary Artery Disease (Including Acute Myocardial Infarction): Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	170.19	0.263	(0.225, 0.306)	0.573	(0.490, 0.666)
	≥60	132.21	0.103	(0.086, 0.123)	0.217	(0.182, 0.258)
EU	18 to 59	141.71	0.192	(0.162, 0.226)	0.418	(0.352, 0.493)
	≥60	42.20	0.039	(0.028, 0.053)	0.083	(0.060, 0.112)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42) and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Conclusion

During preparation of this PBRER, a comprehensive cumulative review for coronary artery disease was conducted by the Company following an epidemiological study based on data from French national databases suggesting a slightly increased risk for myocardial infarction with the Janssen COVID-19 vaccine. Additional information is available in Section 14, Late Breaking Information.

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new safety information was identified during the reporting period for coronary artery disease, including acute myocardial infarction. The Company will continue to closely monitor cases of coronary artery disease, including acute myocardial infarction as an AESI

16.3.6.1.5. Heart Failure

Introduction

Heart failure (HF) 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included (EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 30) and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 98 (63 medically confirmed and 35 medically unconfirmed) cases reporting HF were identified. All 98 cases were serious and reported a total of 112 events (111 serious; 1 nonserious).

Of these 98 cases during the reporting period of 25 August 2021 to 24 February 2022, 20 were reported from Janssen Sponsored Clinical Studies and 78 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 186 (132 medically confirmed and 54 medically unconfirmed) cases reporting HF were identified. All 186 cases were serious and reported a total of 215 events (213 serious; 2 nonserious).

Of these 186 cumulative cases received, 31 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Study, and 153 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 86 below.

Table 86: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Heart Failure

Case Characteristics		Number of Cases Received During the Reporting Period=98	Number of Cases Received Cumulatively=186
Sex	Male	56	95
	Female	36	84
	NR	6	7
Age (Years)[a]	18 to 35	9	15
Minimum: 20	36 to 50	11	31
Maximum: 98	51 to 64	37	67
Mean: 59.7	≥65	33	63
Median: 61	NR	8	10
Source	Spontaneous	78	153
	Clinical study (interventional; non-solicited)	20	33
Country/Territory[b]	United States	53	118
	Germany	11	15
	South Africa	10	15
	Italy	3	3
	Philippines	3	4
	Brazil	2	3
	Chile	2	2
	Estonia	2	2
	Argentina	1	3
	Austria	1	2
	Belgium	1	2
	Colombia	1	2
	Czech Republic	1	1
	France	1	4
	Lao People's Democratic Republic	1	1
	Lesotho	1	1
	Mexico	1	1
	Netherlands	1	1
	Spain	1	2
	Switzerland	1	1
Event Characteristics		**Number of Events=112**	**Number of Events=215**
Seriousness (Event Level)[c]	Serious	111	213
	Nonserious	1	2
Outcome (Event Level)[c]	Not resolved	31	58
	Fatal	25	42
	Resolving	13	23
	Resolved	12	30
	Resolved with	7	8

Table 86: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Heart Failure

Case Characteristics		Number of Cases Received During the Reporting Period=98	Number of Cases Received Cumulatively=186
	sequelae NR	24	54

Key: NR=Not Reported.
a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).
b: Countries/Territories are listed in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

The frequency distribution of the MedDRA PTs of interest reported in cases reporting HF with the use of Ad26.COV2.S is presented in Table 87 below. A single case may contain more than 1 EOI.

Table 87: Frequency of MedDRA PTs in Cases Reporting Heart Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cardiac failure	40	0	65	0
Cardiac failure congestive	20	0	41	0
Pulmonary oedema	13	0	30	0
Cardiogenic shock	9	0	15	0
Ejection fraction decreased	7	1	17	2
Cardiac failure acute	6	0	8	0
Cardiac failure chronic	4	0	5	0
Acute left ventricular failure	3	0	6	0
Cor pulmonale	3	0	7	0
Left ventricular failure	3	0	5	0
Acute pulmonary oedema	2	0	4	0
Chronic left ventricular failure	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 20 cases reporting HF were retrieved from Janssen Sponsored Clinical Studies. Of the 20 cases, 17 were from VAC31518COV3001 and 3 were from VAC31518COV3009. These 20 cases reported 21 serious

EOI. Of these 20 cases, the most frequently reported country/territory of origin was South Africa (n=9). Of these 20 cases, 14 concerned males and 6 females. The age range was 43 to 85 years.

The EOI included cardiac failure (n=10), cardiac failure congestive (n=6), cor pulmonale, cardiac failure acute (n=2 each), and acute pulmonary oedema (n=1). The mean and median TTO was 275.7 days and 306 days, respectively. The outcome of the 21 EOI were reported as resolved (n=9), resolving (n=5), not resolved (n=4), resolved with sequelae (n=2), and fatal (n=1). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=21).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 78 cases reporting HF were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 78 cases reported 90 serious EOI. Of these 78 cases, the most frequently reported country/territory of origin was the US (n=49) followed by Germany (n=11), and Italy and Philippines (n=3 each). Of the 78 cases, 42 cases concerned males, 30 females, and 6 had no sex reported. The age range was 20 to 98 years.

The EOI (≥3) included cardiac failure (n=30), cardiac failure congestive (n=14), pulmonary oedema (n=13), cardiogenic shock (n=9), ejection fraction decreased (n=8), cardiac failure acute, cardiac failure chronic (n=4 each), and acute left ventricular failure and left ventricular failure (n=3 each). The reported mean and median TTO was 89.2 days and 62.5 days, respectively. Where reported (n=67), the outcomes were not resolved (n=27), fatal (n=24), resolving (n=8), resolved with sequelae (n=5), and resolved (n=3). The events with a fatal outcome were cardiac failure (n=6), cardiogenic shock (n=5), ejection fraction decreased, pulmonary oedema (n=3 each), cardiac failure acute, cardiac failure congestive (n=2 each), acute left ventricular failure, cardiac failure chronic, and left ventricular failure (n=1 each).

No ICSR literature cases were retrieved from the search strategy during the reporting period.

Fatal Cases

A total of 26 cases had a fatal outcome, for 6 the event outcome was not reported. A line listing with the patient's main clinical details is provided in Appendix 7.18.1. Of these 26 cases, 1 was reported in multiple unidentifiable patients. Therefore, this case is not discussed further.

Nine cases reported TTO within the risk window of 30 days. Five cases were medically confirmed, and 4 were medically unconfirmed. Patient age was reported in 6 cases and ranged from 24 to 93 years, and TTO was reported in 5 cases and ranged from 1 to 22 days post-vaccination. The

cause of death was reported due to unspecified causes (n=5), cardiac causes (n=3), and multiple organ dysfunction syndrome (n=1). The majority of the cases (8/9, 89%) cases lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment and the remaining 1 case reported an alternative aetiology of metastatic lung carcinoma.

Of the 9 fatal cases of HF within the risk window, 2 were reported in subjects aged <40 years. A summary of these cases is shown below:

- In the first case, a 24-year-old female experienced acute liver failure 6 days following the administration of AD26.COV2.S vaccine and was hospitalised with altered mental status, respiratory distress, and haematemesis. Laboratory tests demonstrated severe lactic acidosis, severe hyperammonemia, and acute renal failure. The patient was diagnosed with multiple organ dysfunction syndrome. Cardiac echo demonstrated acute systolic and diastolic heart failure with reduced ejection fraction and a CT demonstrated diffuse brain oedema and mild cerebellar tonsillar herniation. The patient died 9 days post-vaccination due to brain herniation, acute hepatic failure, and multiple organ dysfunction syndrome. The case had limited information on the patient's medical history, autopsy result, and other risk factors, including concomitant prescribed and over-the-counter medications, for acute liver failure and gastrointestinal bleeding. Considering the compatible TTO after vaccination a causal role of the vaccine cannot be excluded.
- The second case received via social media concerned a 20-year-old male who experienced cardiac failure, kidney failure, and blood clots. The cause of death was unknown. The case lacks essential information regarding the patient's medical history, concomitant medication, the clinical course of events, EKG, diagnostic workup/laboratory results, autopsy result, and TTO precluding any meaningful medical assessment.

Sixteen cases reported TTO outside of the risk window of 30 days. Eleven cases were medically confirmed, and 5 cases were medically unconfirmed. Patient age ranged from 25 to 81years and the TTO ranged from 35 to 313 days post-vaccination. The cause of death was reported due to cardiac causes and COVID-19 infection (n=6), cardiac causes (n=5), splenic rupture, shock (n=1 each), unspecified cause (3). Thirteen cases reported an alternative aetiology/identified risk factor for the development of an EOI. This included underlying cardiac history (n=9), and pulmonary embolus, hypertension, splenic rupture, and obesity (n=1 each). A risk factor of COVID-19 infection was reported in 8 cases. The remaining 3 cases lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Of the 16 fatal cases of HF outside the risk window, 3 were reported in patients aged <40 years. A summary of these cases is shown below:

- In the first case, a 25-year-old patient of unknown sex experienced tonic-clonic seizure 3 days post-vaccination with Ad26.COV2.S and was hospitalised in a postictal state. The neurology

evaluation suggested possible autoimmune encephalitis. The patient died from cardiogenic shock 38 days post-vaccination.

- In a second case, a 29-year-old male experienced acute MI, coronary ostial stenosis, cardiogenic shock, brain oedema, and hypoxic brain damage 105 days post-vaccination with Ad26.COV2.S vaccine, and was hospitalised. The next day, the patient died of cardiogenic shock.
- In the third case, A 30 -year old male with a risk factor of obesity (height and weight details not provided) experienced dyspnoea in the same month of vaccination with Ad26.COV2.S. On day 55 post-vaccination, the patient was hospitalised after a syncopal episode. The patient had acute right coronary artery thrombosis and underwent percutaneous coronary intervention and thrombectomy. The patient was noted to have cardiomyopathy with an EF of less than 20%. Several hours later while in the ICU, the patient experienced seizures followed by pulseless electrical activity arrest presumed pulmonary embolism. The patient died from cardiomyopathy, coronary artery thrombosis, pulmonary embolism, pulseless electrical activity, seizure, syncope, PO2 decreased, and ejection fraction decreased. In addition to the long latency and risk factor of obesity, further information on the result of the autopsy, the patient's complete medical history/concomitant medications, diagnostic workups are needed to confirm the diagnoses and to exclude other causes.

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 heart failure being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 1 (medically confirmed) case was identified reporting heart failure in an individual who received the booster dose. This serious case was homologous. CIOMS II LL is presented in Appendix 7.18.2.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 88.

Table 88: Heart Failure: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

		Broad O/E Analysis			Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	36.86	0.102	(0.072, 0.141)	0.332	(0.233, 0.458)
	≥60	34.04	0.005	(0.003, 0.007)	0.010	(0.007, 0.014)
EU	18 to 59	10.00	0.033	(0.016, 0.061)	0.076	(0.036, 0.140)
	≥60	14.00	0.004	(0.002, 0.006)	0.007	(0.004, 0.012)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 30) and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Conclusion

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

Since launch, no signal for acute nor chronic exacerbated heart disease has been observed for Ad26.COV2.S. Based on this, the Company proposes to monitor these cases through routine pharmacovigilance activities.

16.3.6.2. Immune System Disorders

16.3.6.2.1. Autoimmune Thyroiditis

Introduction

Autoimmune thyroiditis 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.

O/E Analysis

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 365), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 24 (8 medically confirmed and 16 medically unconfirmed) cases reporting autoimmune thyroiditis were identified. Of these cases, 22 were serious and 2 nonserious, and reported a total of 25 events (21 serious; 4 nonserious).

Of these 24 cases during the reporting period of 25 August 2021 to 24 February 2022, 1 was reported from a Janssen Sponsored Clinical Study and 23 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 45 (16 medically confirmed and 29 medically unconfirmed) cases reporting autoimmune thyroiditis were identified. Of these cases, 40 cases were serious and 5 nonserious, and reported a total of 47 events (38 serious; 9 nonserious).

Of these 45 cumulative cases received, 1 was reported from a Janssen Sponsored Clinical Study, and 44 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

An overview of these cases is presented in Table 89 below.

Table 89: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Autoimmune Thyroiditis

Case Characteristics		Number of Cases Received During the Reporting Period=24	Number of Cases Received Cumulatively=45
Sex	Female	16	32
	Male	8	12
	NR	0	1
Age (Years)[a]	18 to 35	10	13
Minimum: 21	36 to 50	5	15
Maximum: 70	51 to 64	6	11
Mean: 40.5	≥65	1	2
	Adult	1	2

Table 89: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Autoimmune Thyroiditis

Case Characteristics		Number of Cases Received During the Reporting Period=24	Number of Cases Received Cumulatively=45
Median: 38	NR	1	2
Source	Spontaneous	23	44
	Clinical study (interventional; non-solicited)	1	1
Country/Territory[b]	United States	8	22
	Germany	5	6
	Netherlands	4	9
	Korea, Republic of	3	3
	Greece	1	1
	Ireland	1	1
	Lithuania	1	1
	Philippines	1	1
Event Characteristics		**Number of Events=25**	**Number of Events=47**
Seriousness (Event Level)[c]	Serious	21	38
	Nonserious	4	9
Outcome (Event Level)[c]	Not resolved	13	29
	Resolving	3	6
	Resolved	2	4
	Resolved with sequelae	1	1
	NR	6	7

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in decreasing frequency for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in these 24 cases reporting autoimmune thyroiditis with the use of Ad26.COV2.S is presented in Table 90 below. A single case may contain more than 1 EOI.

Table 90: Frequency of MedDRA PTs in Cases Reporting Autoimmune Thyroiditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Basedow's disease	10	0	19	0
Autoimmune thyroiditis	7	0	12	0
Thyroiditis	1	3	1	8
Thyroiditis acute	2	0	3	0

Table 90: Frequency of MedDRA PTs in Cases Reporting Autoimmune Thyroiditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Addison's disease	1	0	2	0
Thyroiditis subacute	0	1	1	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing frequency for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting autoimmune thyroiditis was retrieved from a Janssen Sponsored Clinical Study. This single case was from VAC31518COV3009. This case reported 1 serious EOI of acute thyroiditis from the [redacted] which concerned a 70-year-old male with pre-existing hypothyroidism on treatment with levothyroxine. The TTO reported was 327 days from the first dose. The outcome for this event was reported as resolving. The Sponsor and Investigator's causality assessment of the EOI was reported as not related.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 23 cases reporting autoimmune thyroiditis were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 23 cases reported 20 serious EOI. Of these 23 cases, the most frequently reported country/territory of origin was the US (n=8) followed by Germany (n=5), and the Netherlands (n=4). Of the 23 cases, 16 concerned females and 7 males. The age range was 21 to 61 years.

The EOI included Basedow's disease (n=10), autoimmune thyroiditis (n=7), thyroiditis (n=4), Addison's disease, thyroiditis acute, and thyroiditis subacute (n=1 each). The reported mean and median TTO were 27 days and 18 days, respectively. Where reported (n=18), the outcomes were not resolved (n=13), resolved (n=2), resolving (n=2), and resolved with sequelae (n=1).

In the majority of cases (n=11) it was not possible to determine whether the reported EOI was a new onset or aggravation of pre-existing disease, as no information was reported with regards to the patients' medical history. TTO ranged from same day to 89 days (mean 25.9; median 14 days). There was no information reported the patients needing thyroid replacement therapy or any other

treatment medication for the event.

Five cases reported a pre-existing thyroid disorder in the patients' medical history. TTO ranged from 6 to 29 days (mean 19.8; median 22 days). None of these cases reported thyroid replacement therapy for the event, treatment medication in 2 cases included methimazole.

In 7 cases ,the patient did not have a history of thyroid disorder and the EOI was considered a new onset. TTO ranged from same day to 91 days (mean 36.7; median 30 days). In 1 case, a 35-year-old female with an underlying polycystic ovary syndrome experienced autoimmune thyroiditis, 91 days post-vaccination, and treatment included levothyroxine. The EOI outcome was reported as not resolved. In the remaining 6 cases, the patients' either did not receive thyroid replacement therapy for the EOI or treatment details were not reported. No cases of autoimmune thyroiditis with a fatal outcome were received during the reporting period or cumulatively.

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed. From the 3 literature cases, 2 patients experienced the EOI 14 days post-vaccination, with thyroid function showing normal before vaccination. One patient had a pre-existing Graves' disease. Diagnosis in both cases was supported by laboratory workup and imaging. It was not reported whether the EOI required thyroid replacement therapy. Outcome of the EOI was not reported. Considering the short TTO a causal relationship with Ad26.COV2.S cannot be excluded.

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

Booster Dose

Cumulatively, 1 serious (medically unconfirmed) case was identified reporting autoimmune thyroiditis in an individual who received the booster dose. This case was homologous. CIOMS II LL is presented in Appendix 7.19.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 91.

Table 91: Autoimmune Thyroiditis: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	18.30	0.009	(0.005, 0.014)	0.052	(0.031, 0.082)
	≥60	3.67	0.002	(0.000, 0.005)	0.009	(0.002, 0.023)
EU	18 to 59	17.84	0.009	(0.006, 0.015)	0.056	(0.033, 0.089)
	≥60	0.15	0.000	(0.000, 0.003)	0.001	(0.000, 0.013)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 365), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis was not required.

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

Conclusion

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

No signals have been identified for autoimmune thyroiditis since launch for Ad26.COV2.S and reported cases are well within expected rates. The Company proposes to discuss this AESI alongside other autoimmune disease flares in future PBRERs within the update for the Missing Information in subjects with Autoimmune or Inflammatory Disorders.

16.3.6.2.2. Type 1 Diabetes Mellitus

Introduction

Type 1 diabetes mellitus 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 365), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 26 (9 medically confirmed and 17 medically unconfirmed) cases reporting type 1 diabetes mellitus were identified. All 26 cases were serious and reported a total of 26 serious events.

Of these 26 cases during the reporting period of 25 August 2021 to 24 February 2022, 4 were reported from Janssen Sponsored Clinical Studies and 22 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 44 (18 medically confirmed and 26 medically unconfirmed) cases reporting type 1 diabetes mellitus were identified. All 44 cases were serious and reported a total of 44 serious events

Of these 44 cumulative cases received, 4 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 39 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 92 below.

Table 92: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Type 1 Diabetes Mellitus

Case Characteristics		Number of Cases Received During the Reporting Period=26	Number of Cases Received Cumulatively=44
Sex	Male	16	26
	Female	9	17
	NR	1	1
Age (Years)[a]	18 to 35	4	9
Minimum: 18	36 to 50	3	6
Maximum: 86	51 to 64	10	16
Mean: 53.7	≥65	6	8
	Adult	2	3

Table 92: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Type 1 Diabetes Mellitus

Case Characteristics		Number of Cases Received During the Reporting Period=26	Number of Cases Received Cumulatively=44
Median: 58	NR	1	2
Source	Spontaneous	21	38
	Clinical study (interventional; non-solicited)	4	5
	Clinical study (non-interventional; solicited)	1	1
Country/Territory[b]	United States	12	24
	Netherlands	4	4
	Germany	3	4
	South Africa	3	5
	Austria	1	1
	Czech Republic	1	1
	Italy	1	1
	Philippines	1	1
Event Characteristics		**Number of Events=26**	**Number of Events=44**
Seriousness (Event Level)[c]	Serious	26	44
Outcome (Event Level)[c]	Not resolved	16	23
	Fatal	3	4
	Resolving	2	5
	Resolved with sequelae	2	2
	Resolved	0	1
	NR	3	9

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting type 1 diabetes mellitus with the use of Ad26.COV2.S is presented in Table 93 below.

Table 93: Frequency of MedDRA PTs in Cases Reporting Type 1 Diabetes Mellitus With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Diabetes mellitus	18	0	32	0
Type 1 diabetes mellitus	8	0	12	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 4 cases reporting type 1 diabetes mellitus were retrieved from Janssen Sponsored Clinical Studies. Of the 4 cases, 3 were reported from VAC31518COV3001 and 1 from VAC31518COV3009. These 4 cases reported 4 serious EOI. Of these 4 cases, the most frequently reported country/territory of origin was South Africa (n=3). Of these 4 cases, 3 concerned females and 1 male. The age range was 58 to 70 years.

The EOI included diabetes mellitus (n=3) and type 1 diabetes mellitus (n=1). The mean and median TTO was 272.8 days and 329 days, respectively. The outcome of the 4 EOI were reported as not resolved (n=3) and fatal (n=1). The fatal case involved a 70-year-old female who experienced the EOI, 416 days post-vaccination, which is outside the risk window for this AESI. The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=4).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 22 cases reporting type 1 diabetes mellitus were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 22 cases reported 22 serious EOI. Of these 22 cases, the most frequently reported country/territory of origin was the US (n=11) followed by the Netherlands (n=4), and Germany (n=3). Of the 22 cases, 15 concerned males, 6 females, and 1 had no sex reported. The age range was 18 to 86 years.

The EOI included diabetes mellitus (n=15) and type 1 diabetes mellitus (n=7). The reported mean and median TTO was 63.2 days and 38 days, respectively. Where reported (n=19), the outcomes were not resolved (n=13), fatal, resolved with sequelae, and resolving (n=2 each). The events with a fatal outcome were diabetes mellitus (n=1) and type 1 diabetes mellitus (n=1).

In half of the cases (n=11) it was not possible to determine whether the reported EOI was a new onset or aggravation of underlying diabetes mellitus, as no information was reported on medical history. TTO ranged from 1 to 201 days (mean 51; median 24 days). Three cases specified the event as type 1 diabetes mellitus. One case reported a concurrent COVID-19 infection which might have contributed to the fatal outcome. The cases were lacking information on medical history, concomitant medication, and detailed clinical course with laboratory workup, which makes the medical assessment difficult.

Four cases reported a history of pre-existing diabetes mellitus. TTO ranged from 5 to 159 days (mean 105.3; median 152 days). The type of diabetes mellitus was not specified in 3 cases. Two patients required insulin treatment. Two cases were confounded by a concurrent COVID-19 infection, which might have contributed to the onset of hyperglycaemia.

In 7 cases, new onset of diabetes mellitus was reported. TTO ranged from 21 to 119 days (mean 72.4; median 61 days). The type of diabetes mellitus was not specified in 5 cases, with 1 patient needing insulin for the EOI.

No ICSR literature cases were retrieved from the search strategy during the reporting period.

Fatal Cases

There were 2 fatal cases with medical history not reported in either case; therefore, it could not be determined whether the EOI was a new onset or aggravation of a pre-existing disease. TTO was 56 days post-vaccination in 1 case and not reported in the other. Both cases were lacking details on medical history, concomitant medication, and detailed clinical course with laboratory workup, which makes the medical assessment difficult.

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 type 1 diabetes mellitus being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 2 serious (1 medically confirmed and 1 medically unconfirmed) cases were identified reporting type 1 diabetes mellitus in individuals who received the booster dose. Of these cases, 1 was heterologous and 1 was homologous. CIOMS II LL is presented in Appendix 7.20.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 94.

Table 94: Type 1 Diabetes Mellitus: Broad O/E and Sensitivity Analysis results (Cumulative to 24 February 2022)

Broad O/E analysis					Sensitivity analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	16.30	0.007	(0.004, 0.012)	0.015	(0.009, 0.024)
	≥60	6.67	0.004	(0.001, 0.008)	0.007	(0.003, 0.015)
EU	18 to 59	8.84	0.005	(0.002, 0.009)	0.010	(0.005, 0.020)
	≥60	3.15	0.005	(0.001, 0.015)	0.013	(0.003, 0.036)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 365), and where time-to-onset was day 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database both during the period and cumulatively, and an O/E, no new critical safety information was identified during the reporting period for type 1 diabetes mellitus.

Based on the lack of signals since launch, the Company proposes to monitor these cases through routine pharmacovigilance activities.

16.3.6.3. Musculoskeletal Disorders

16.3.6.3.1. Acute Aseptic Arthritis

Introduction

Acute aseptic arthritis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60 years. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 365), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations [for initial and booster doses], risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 200 (100 medically confirmed and 100 medically unconfirmed) cases reporting acute aseptic arthritis were identified. Of these cases, 133 were serious and 67 nonserious, and reported a total of 206 events (131 serious; 75 nonserious).

Of these 200 cases during the reporting period of 25 August 2021 to 24 February 2022, 38 were reported from Janssen Sponsored Clinical Studies and 162 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 468 (285 medically confirmed and 183 medically unconfirmed) cases reporting acute aseptic arthritis were identified. Of these cases, 234 cases were serious and 234 nonserious, and reported a total of 484 events (216 serious; 268 nonserious).

Of these 468 cumulative cases received, 54 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Study, and 412 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 95 below.

Table 95: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics		Number of Cases Received During the Reporting Period=200	Number of Cases Received Cumulatively=468
Sex	Female	120	239
	Male	69	206
	NR	11	23
Age (Years)[a]	18 to 35	17	36
Minimum: 22	36 to 50	48	168
Maximum: 82	51 to 64	70	135
Mean: 54.5	≥65	45	90
	Adult	5	7

Table 95: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics		Number of Cases Received During the Reporting Period=200	Number of Cases Received Cumulatively=468
Median: 56	Elderly	2	2
	NR	13	30
Source	Spontaneous	156	401
	Clinical study (interventional; non-solicited)	38	56
	Clinical study (non-interventional; solicited)	4	8
	Clinical study (non-interventional; non-solicited)	2	3
Country/Territory[b]	United States	85	189
	Germany	27	30
	France	15	21
	Korea, Republic of	12	136
	Netherlands	9	18
	Belgium	8	11
	Brazil	8	8
	South Africa	8	12
	Spain	4	7
	Colombia	3	4
	Argentina	2	2
	Austria	2	2
	Czech Republic	2	2
	Greece	2	2
	Italy	2	7
	United Kingdom	2	2
Event Characteristics		**Number of Events=206**	**Number of Events=484**
Seriousness (Event Level)[c]	Nonserious	75	268
	Serious	131	216
Outcome (Event Level)[c]	Not resolved	85	154
	Resolved	43	96
	Resolving	30	49
	Resolved with sequelae	3	4
	Fatal	2	2
	NR	43	179

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

Table 95: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics	Number of Cases Received During the Reporting Period=200	Number of Cases Received Cumulatively=468

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

The frequency distribution of the MedDRA PTs of interest reported in cases reporting acute aseptic arthritis with the use of Ad26.COV2.S is presented in Table 96 below. A single case may contain more than 1 EOI.

Table 96: Frequency of MedDRA PTs in Cases Reporting Acute Aseptic Arthritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Arthritis	13	43	24	208
Osteoarthritis	39	8	52	11
Rheumatoid arthritis	39	0	67	0
Gout	3	8	5	18
Polyarthritis	9	0	12	0
Rheumatic disorder	1	7	1	9
Periarthritis	3	3	9	10
Temporomandibular joint syndrome	1	5	1	7
Spinal osteoarthritis	5	0	11	1
Arthritis reactive	4	0	7	0
Still's disease	4	0	7	0
Ankylosing spondylitis	3	0	4	0
Autoimmune arthritis	3	0	3	0
Facet joint syndrome	2	0	5	0
Chondrocalcinosis	1	0	1	0
Injection site joint inflammation	0	1	0	1
Spondylitis	1	0	1	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 38 cases reporting acute

aseptic arthritis were retrieved from Janssen Sponsored Clinical Studies. Of the 38 cases, 22 were from VAC31518COV3001, 13 from VAC31518COV3009, 2 from VAC31518COV1001, and 1 from VAC31518COV2008. These 38 cases reported 37 serious EOI. Of these 38 cases, the most frequently reported country/territory of origin was the US (n=15). Of these 38 cases, 22 concerned females and 16 males. The age range was 44 to 76 years.

The EOI included osteoarthritis (n=34) and 1 each of arthritis, gout, rheumatoid arthritis, and spinal osteoarthritis. The mean and median TTO was 236.9 days and 246 days, respectively. The outcome of the 38 EOI were reported as resolved (n=30), resolving (n=4), not resolved (n=2), and resolved with sequelae (n=2). The Sponsor and Investigator's causality assessment of the EOI was reported as not related for all cases (n=38).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 162 cases reporting acute aseptic arthritis were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 162 cases reported 94 serious EOI. Of these 162 cases, the most frequently reported country/territory of origin was the US (n=70) followed by Germany (n=27), and France and Korea Republic of (n=12 each). Of the 162 cases, 98 concerned females, 53 males, and 11 had no sex reported. The age range was 22 to 82 years.

The EOI (n≥6) included arthritis (n=55), rheumatoid arthritis (n=38), osteoarthritis (n=13), gout (n=10), polyarthritis (n=9), rheumatic disorder (n=8), and periarthritis and temporomandibular joint syndrome (n=6 each). The reported mean and median TTO was 44.7 days and 8.5 days, respectively. Where reported (n=125), the outcomes were not resolved (n=83), resolving (n=26), resolved (n=13), fatal (n=2), and resolved with sequelae (n=1). The events with a fatal outcome were rheumatoid arthritis and spinal osteoarthritis (n=1 each).

Three ICSR literature cases were received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information of acute aseptic arthritis.

Fatal Cases

Two fatal cases were reported during the interval that included the serious EOI of spinal osteoarthritis and rheumatoid arthritis, respectively. These 2 cases reported TTO within the risk window of 365 days. Both cases were medically confirmed. The patients were 81- and 52-year-old respectively, both were male and the TTO was 235 days post-vaccination for the first case and 249 days post-vaccination for the second case. For both cases the cause of death was listed as

COVID-19 complications and not the EOI. It was unspecified if an autopsy was performed in both cases.

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 acute aseptic arthritis being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 7 (2 medically confirmed and 5 medically unconfirmed) cases were identified reporting acute aseptic arthritis in individuals who received the booster dose. There were 3 serious and 4 nonserious cases. All 7 cases were homologous. CIOMS II LL is presented in Appendix 7.21.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 97.

Table 97: Acute Aseptic Arthritis: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	94.32	0.091	(0.074, 0.111)	0.219	(0.177, 0.267)
	≥60	69.42	0.181	(0.141, 0.229)	0.435	(0.339, 0.550)
EU	18 to 59	69.11	0.004	(0.003, 0.005)	0.008	(0.006, 0.010)
	≥60	27.82	0.002	(0.001, 0.003)	0.004	(0.003, 0.005)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 365), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new safety information was identified during the reporting period for acute aseptic arthritis. The Company will continue to closely monitor this event as an AESI. Updates for flares of rheumatoid arthritis as well as other autoimmune musculoskeletal and connective tissue disorders will be presented in future PBRERs within the update for the Missing Information in subjects with Autoimmune or Inflammatory Disorders.

16.3.6.4. Nervous System Disorders

16.3.6.4.1. Bell's Palsy

Introduction

Bell's palsy is listed as an AESI in the cRMP, EU RMP, and US PVP.

A pooled analysis of the double-blind phases of 5 Company-sponsored trials (COV1001, COV1002, COV2001, COV3001, and COV3009) conducted by the Company at the time of the preparation of this PBRER showed a numerical imbalance between Ad26.COV2.S (n=4) and placebo (n=1). A cumulative assessment of available safety data has been carried out as a result of this imbalance.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases of Bell's palsy and facial paralysis received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 42), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 184 (74 medically confirmed and 110 medically unconfirmed) cases reporting Bell's palsy and facial paralysis were identified. Of these cases, 171 were serious and 13 nonserious, and reported a total of 193 events (176 serious; 17 nonserious).

Of these 184 cases during the reporting period of 25 August 2021 to 24 February 2022, 4 were

reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 179 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 405 (197 medically confirmed and 208 medically unconfirmed) cases reporting Bell's palsy were identified. Of these cases, 387 were serious and 18 nonserious, and reported a total of 436 events (408 serious; 28 nonserious).

Of these 405 cumulative cases received, 7 were reported from Janssen Sponsored Clinical Studies, 9 from Janssen Supported Clinical Studies, and 389 from Post-marketing Sources (including spontaneous, and solicited cases.

An overview of these cases is presented in Table 98 below.

Table 98: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Bell's Palsy

Case Characteristics		Number of Cases Received During the Reporting Period=184	Number of Cases Received Cumulatively=405
Sex	Male	103	225
	Female	71	165
	NR	10	15
Age (Years)[a]	18 to 35	28	63
Minimum:21	36 to 50	59	128
Maximum:81	51 to 64	63	134
Mean:49.1	≥65	18	46
Median:50	Adult	0	1
	NR	16	33
Source	Spontaneous	179	389
	Clinical study (interventional; non-solicited)	5	15
	Clinical study (non-interventional; non-solicited)	0	1
Country/Territory[b]	United States	73	207
	Germany	43	63
	Netherlands	12	21
	Austria	6	9
	France	6	13
	Italy	6	15
	Brazil	5	13
	Portugal	4	5
	Belgium	3	5
	Croatia	3	3
	Philippines	3	4
	Czech Republic	2	2
	Ireland	2	4

Table 98: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Bell's Palsy

Case Characteristics		Number of Cases Received During the Reporting Period=184	Number of Cases Received Cumulatively=405
	Korea, Republic of	2	2
	Lithuania	2	2
	Romania	2	2
	South Africa	2	10
	Spain	2	11
	Switzerland	2	2
	Egypt	1	1
	Estonia	1	1
	Greece	1	2
	Luxembourg	1	1
Event Characteristics		**Number of Events=193**	**Number of Events=436**
Seriousness (Event Level)[c]	Serious	176	408
	Nonserious	17	28
Outcome (Event Level)[c]	Not resolved	93	224
	Resolved	31	60
	Resolving	27	60
	Resolved with sequelae	5	6
	Fatal	2	3
	NR	35	83

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in descending order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting Bell's palsy with the use of Ad26.COV2.S is presented in Table 99 below. A single case may contain more than 1 EOI.

Table 99: Frequency of MedDRA PTs in Cases Reporting Bell's Palsy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Facial paralysis	103	0	234	0
Bell's palsy	55	0	121	0

Table 99: Frequency of MedDRA PTs in Cases Reporting Bell's Palsy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Facial paresis	18	14	53	24
Facial spasm	0	3	0	3
Facial nerve disorder	0	0	0	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by descending order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 4 cases reporting Bell's palsy were retrieved from Janssen Sponsored Clinical Studies. All 4 cases were from VAC31518COV3001. These 4 cases reported 4 serious EOI. Of these 4 cases, the most frequently reported country/territory of origin was Brazil (n=2) followed by South Africa (n=1), and the US (n=1). Of these 4 cases, 3 concerned females and 1 male. The age range was 52 to 65 years.

The EOI (n≥2) included Bell's palsy (n=2). The mean and median TTO of the 4 EOI was 279.8 days and 272 days, respectively. The outcome of the 4 EOI was reported as resolved (n=3) and resolved with sequelae (n=1). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=4).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting Bell's palsy was retrieved from a Janssen Supported Clinical Study. The case was from VAC31518COV3012 (Sisonke) and concerned a 66-year-old [redacted] from South Africa who experienced a serious EOI of Bell's palsy. The TTO was 31 days, and the outcome was reported as not resolved. Company causality was assessed as related and the Sponsor's causality was assessed as possible.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 179 cases reporting Bell's palsy were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 179 cases reported 171 serious EOI. Of these 179 cases, the most frequently reported country/territory of origin was the US (n=72) followed by Germany (n=43), and the Netherlands (n=12). Of the 179 cases, 102 concerned males, 67 females, and 10 had no sex reported. The age range was 21 to 81 years.

The EOI (n>30) included facial paralysis (n=102), Bell's palsy (n=52), and facial paresis (n=31).

The reported mean and median TTO was 31.4 days and 14 days, respectively. Where reported (n=153), the outcomes were not resolved (n=92), resolved (n=28), resolving (n=27), resolved with sequelae (n=4), and fatal (n=2). Both EOI with a fatal outcome were facial paralysis.

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed and 2 cases were identified reporting the EOI. One case concerned a 44-year-old female who experienced transverse myelitis with intact cranial nerves II-XII who developed Bell's palsy while undergoing plasma exchange. The other case concerned multiple patients (9 male, 3 female). Events were reported as cerebral venous sinus thrombosis, damage to the plexus brachialis or lumbosacralis, encephalitis, facial paresis, GBS, myelitis, myositis, myocarditis, pericarditis, and vaccine-induced thrombotic thrombocytopenia. Both cases lacked pertinent information (medical history, TTO, clinical course, treatment of EOI, and diagnostic testing), precluding medical assessment. Additionally, both cases reported concurrent events that may have contributed to the EOI.

Fatal Cases

During this reporting period, 2 fatal cases (both medically confirmed) reporting EOI were retrieved from Post-marketing sources. However, in both cases clinical details were not consistent with Bell's palsy, as the patient's symptoms were likely associated with cerebrovascular disease. There were 2 EOI, both serious, reported in these cases. One case concerned a 67-year-old female who experienced facial paralysis (reported as facial dropping), and the TTO was within the risk window of 42 days for Bell's palsy. The patient died on an unspecified date and the causes of death were reported as facial dropping, slurred speech, and body weakness. The other case concerned a 54-year-old male who experienced mental status changes, facial paralysis (reported as facial droop), and transient cerebral ischaemic attack. The TTO was outside the risk window of 42 days for Bell's palsy. The patient subsequently died with the causes of death reported as facial paralysis, transient ischaemic attack, and mental status changes.

Both cases lack pertinent information (medical history, concurrent conditions, concomitant medications, clinical course and treatment for the EOI, diagnostic testing, and autopsy results), precluding meaningful medical assessment. Based on the information provided, facial paralysis in these cases was more likely associated with cerebrovascular accident than with Bell's palsy.

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 Bell's palsy being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 5 serious cases (all medically confirmed) were identified reporting Bell's palsy in individuals who received the booster dose. Of these cases, 3 were heterologous and 2 were homologous. CIOMS II LL is presented in Appendix 7.22.1

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 100.

Table 100: Bell's Palsy: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	125.32	0.077	(0.064, 0.091)	0.180	(0.150, 0.214)
	≥60	57.42	0.060	(0.046, 0.078)	0.121	(0.092, 0.156)
EU	18 to 59	126.52	0.248	(0.207, 0.295)	0.504	(0.420, 0.600)
	≥60	20.45	0.143	(0.088, 0.220)	0.294	(0.181, 0.452)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Data Mining Results

Data mining was performed to determine if there was a statistical association between the Janssen COVID-19 vaccine (Ad26.COV2.S) and the PTs Bell's palsy or Facial paralysis (and their combination) using multiple spontaneous data sources:

- Janssen's global safety database
- FDA VAERS
- EudraVigilance

The data mining search for both the custom term (combining both PTs of Bell's palsy and Facial paralysis), and the individual PT Bell's palsy met the statistical threshold for disproportionality with the Janssen COVID-19 vaccine when compared to all products in the Company global safety database. Similarly, both individual PTs Bell's palsy and Facial paralysis met the statistical threshold for disproportionality with the Janssen COVID-19 vaccine when compared to all products in EudraVigilance. The analysis did not meet the statistical threshold for disproportionality with the Janssen COVID-19 vaccine when compared to all vaccines in VAERS.

Additional information on the evaluation can be found in Appendix 7.22.2.

Conclusion

The Company performed a cumulative analysis of the available safety data following the numerical imbalance observed in the pooled primary analysis of studies COV1001, COV1002, COV2001, COV3001, and COV3009.

Based on the totality of the data, the Company has concluded there is a reasonable possibility of a causal association between Ad26.COV2.S and facial paralysis. Important factors for this decision are:

- Biological plausibility
- Key cases (both in CT and PM) in close temporal association with no clear confounders
- Numerical imbalance in CTs and disproportionate reporting in PM

The CCDS will be amended to include facial paralysis as an adverse reaction. The Company will continue to monitor cases of facial paralysis/Bell's palsy through routine pharmacovigilance activities.

16.3.6.4.2. Convulsions/Seizures

Introduction

Convulsions/seizures are included in the list AESI as described in the cRMP, EU RMP, and 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 14), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 169 (74 medically confirmed and 95 medically unconfirmed) cases reporting convulsions/seizures were identified. Of these cases, 167 were serious and 2 nonserious, and reported a total of 178 events (174 serious;

4 nonserious).

Of these 169 cases during the reporting period of 25 August 2021 to 24 February 2022, 4 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 162 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 404 (202 medically confirmed and 202 medically unconfirmed) cases reporting convulsions/seizures were identified. Of these cases, 397 cases were serious and 7 nonserious, and reported a total of 422 events (410 serious; 12 nonserious).

Of these 404 cumulative cases received, 6 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 390 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 101 below.

Table 101: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Convulsions/Seizures

Case Characteristics		Number of Cases Received During the Reporting Period=169	Number of Cases Received Cumulatively=404
Sex	Male	99	216
	Female	62	161
	NR	8	27
Age (Years)[a]	0 to 17	1	1
Minimum: 16	18 to 35	83	175
Maximum: 79	36 to 50	32	87
Mean: 36.5	51 to 64	25	52
Median: 33	≥65	7	29
	Adult	2	6
	Elderly	0	1
	Neonate	1	1
	NR	18	52
Source	Spontaneous	161	386
	Clinical study (interventional; non-solicited)	7	13
	Clinical study (non-interventional; solicited)	1	4
	Clinical study (non-interventional; non-solicited)	0	1
Country/Territory[b]	United States	52	170
	Germany	24	31
	Philippines	11	16
	Romania	8	10

Table 101: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Convulsions/Seizures

Case Characteristics		Number of Cases Received During the Reporting Period=169	Number of Cases Received Cumulatively=404
	Netherlands	7	19
	Austria	6	11
	Greece	6	7
	Poland	6	19
	Portugal	6	21
	South Africa	6	10
	Ireland	5	11
Event Characteristics		**Number of Events=178**	**Number of Events=422**
Seriousness (Event Level)[c]	Serious	174	410
	Nonserious	4	12
Outcome (Event Level)[c]	Resolved	62	159
	Not resolved	19	55
	Resolving	18	34
	Fatal	11	17
	Resolved with sequelae	8	11
	NR	60	146

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥5 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting convulsions/seizures with the use of Ad26.COV2.S is presented in Table 102 below. A single case may contain more than 1 EOI.

Table 102: Frequency of MedDRA PTs in Cases Reporting Convulsions/Seizures With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Seizure	101	0	289	1
Epilepsy	30	0	38	0
Generalised tonic-clonic seizure	19	0	34	0
Partial seizures	6	0	8	0
Seizure like phenomena	5	0	8	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest with frequency ≥5 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 4 cases reporting convulsions/seizures were retrieved from Janssen Sponsored Clinical Studies. Three cases were from VAC31518COV3001, and 1 from VAC31518COV3009. These 4 cases reported 4 serious EOI. Of these 4 cases, the most frequently reported country/territory of origin was the US (n=2), followed by South Africa and Columbia (n=1 each). These 4 cases concerned 3 males and 1 female. The age range was 29 to 76 years.

The EOI included epilepsy (n=2), and partial seizures and post-traumatic epilepsy (n=1 each). The mean and median TTO was 294 days and 354 days, respectively. Where reported (n=4), the outcomes were resolved (n=2), and not resolved and fatal (n=1 each). The Sponsor and Investigator's causality assessments of the EOI were all reported as not related (n=4).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 3 cases reporting convulsions/seizures were retrieved from Janssen Supported Clinical Studies. Two cases were from VAC31518COV3021 and 1 from VAC31518COV3012 (Sisonke). These 3 cases reported a total of 3 serious EOI. All 3 cases were reported from South Africa and concerned 2 females and 1 male. The age range was 35 to 57 years.

The EOI included seizure (n=2) and epilepsy (n=1). The mean and median TTO were both 1 day. The outcome of the 3 events was reported as resolving (n=2) and resolved (n=1). The Company and Sponsor's causality assessments of the EOI were reported as not related (n=3).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 162 cases reporting convulsions/seizures were retrieved from Post-marketing sources (including spontaneous and

solicited cases). These 162 cases reported a total of 167 serious EOI. Of these 162 cases, the most frequently reported country/territory of origin was the US (n=50) followed by Germany (n=24). Of the 162 cases, 95 concerned males, 59 females, and 8 had no sex reported. The age range was 16 to 79 years.

The EOI included seizure (n=99), epilepsy (n=27), and generalised tonic-clonic seizure (n=19). The reported mean and median TTO was 12.4 days and 1 day, respectively. Where reported (n=111), the outcomes were resolved (n=59), not resolved (n=18), resolving (n=16), fatal (n=10), and resolved with sequelae (n=8). The events with a fatal outcome were seizure (n=6), febrile convulsion (n=2), and seizure like phenomena and status epilepticus (n=1 each).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed. One case was retrieved that concerned a 21-year-old female who experienced initial symptoms of fever, chills, and photophobia 2 weeks post-vaccination with Ad26.COV2.S, and experienced seizure activity on an unspecified date. The EOI occurred in the context of underlying COVID-19 infection and resultant MIS-C with progressive encephalopathy, which may have contributed to and provide alternate aetiologies for seizures. Additionally, lack of information regarding the seizure activity (including TTO, clinical course, treatment, and outcome of the EOI) precludes meaningful medical assessment.

Fatal Cases

During the reporting period of 25 August 2021 to 24 February 2022, 8 fatal cases (all medically confirmed) reporting 10 EOI with a fatal outcome were retrieved. These events were seizure (n=6), febrile convulsion (n=2), and seizure like phenomena and status epilepticus (n=1 each). In 3 of the 8 fatal cases, seizure (n=3) was reported in 2 males and 1 female with ages that ranged from 30 to 76 years. TTO of the EOI was 41 to 70 days, which is outside the 14-day risk window for convulsions/seizures. In 2 cases, 4 EOI were reported: seizure (n=2), seizure like phenomena (n=1) and status epilepticus (n=1). In both cases, these EOI occurred in the context of multiple concurrent conditions (cerebellar stroke, cerebral haemorrhage, cerebral infarction, cerebral mass effect, hydrocephalus, ischaemic stroke, posterior fossa syndrome, subarachnoid haemorrhage, superior sagittal sinus thrombosis, and thalamic infarction), which may have contributed to and/or provide alternate aetiologies for the EOI. In the remaining 3 cases, EOI were reported as febrile convulsion (n=2) and seizure (n=1). These cases lacked information regarding medical history, concurrent conditions, concomitant medications, clinical course, diagnostic testing, treatment and autopsy results, precluding meaningful medical assessment.

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

Booster Dose

Cumulatively, 5 serious (4 medically confirmed and 1 medically unconfirmed) cases were identified reporting convulsions/seizures in individuals who received the booster dose. Of these cases, 3 were homologous and 2 were heterologous. CIOMS II LL is presented in Appendix 7.23.

O/E Analysis Results

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

Table 103: Generalised Convulsions: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	106.43	0.398	(0.326, 0.481)	0.795	(0.651, 0.961)
	≥60	37.15	0.170	(0.120, 0.234)	0.340	(0.239, 0.468)
EU	18 to 59	139.95	0.556	(0.468, 0.656)	1.265	(1.064, 1.493)
	≥60	10.97	0.067	(0.033, 0.120)	0.147	(0.073, 0.263)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 14), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 for both age groups in the US and EU. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US for both age groups. In the EU, the O/E ratio was >1 in the 18 to 59 age group only.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was > 1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the window (day: 1 to 14) only. Results of the restricted O/E and sensitivity analysis for generalised convulsions are presented in Table 104.

Table 104: Generalised Convulsions: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Restricted O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
EU	18 to 59	31.76	0.126	(0.086, 0.178)	0.287	(0.196, 0.406)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 4) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) and sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 for the EU 18 to 59 age group.

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

Conclusion

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

16.3.6.4.3. 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 US PVP.

On 23 September 2021, a signal was identified for transverse myelitis and encephalitis (including acute disseminated encephalomyelitis) with the use of COVID-19 vaccine AD26.COV2.S based on the EMA PRAC Assessment Report for the August 2021 Monthly SSR. The evaluation method included a cumulative case series review of available data in the Company global safety database through 31 August 2021 and is presented in Section 16.2.1.1.3.

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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU stratified by age groups: 18 to 59 and ≥ 60 years old. Based on available background incidence rates, an analysis was performed separately for encephalitis (including acute disseminated encephalomyelitis), and acute disseminated encephalomyelitis alone. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1-42), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group. To note, the PT of Photophobia was excluded from the search criteria for encephalitis (including acute disseminated encephalomyelitis; see Appendix 6.1 for full methodology to include: exposure

calculations, risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 127 (48 medically confirmed and 79 medically unconfirmed) cases reporting encephalitis (including ADEM and meningoencephalitis) were identified. Of these cases, 97 were serious and 30 nonserious, and reported a total of 132 events (95 serious; 37 nonserious).

Of these 127 cases during the reporting period of 25 August 2021 to 24 February 2022, 4 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 122 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 297 (126 medically confirmed and 171 medically unconfirmed) cases reporting encephalitis (including ADEM and meningoencephalitis) were identified. Of these cases, 223 were serious and 74 nonserious, and reported a total of 309 events (216 serious; 93 nonserious).

Of these 297 cumulative cases received, 8 were reported from Janssen Sponsored Clinical Studies, 5 from Janssen Supported Clinical Studies, and 284 from Post-marketing Sources (including spontaneous and solicited cases.

An overview of these cases is presented in Table 105 below.

Table 105: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis (Including ADEM and Meningoencephalitis)

Case Characteristics		Number of Cases Received During the Reporting Period=127	Number of Cases Received Cumulatively=297
Sex	Female	72	168
	Male	51	120
	NR	4	9
Age (Years)[a]	0 to 17	1	1
Minimum:17	18 to 35	38	91
Maximum:98	36 to 50	41	95
Mean:45.5	51 to 64	15	46
Median:43	≥65	21	41
	Adult	1	1
	Elderly	2	2
	NR	8	20
Source	Spontaneous	114	273
	Clinical study (non-interventional; solicited)	8	11
	Clinical study (interventional; non-solicited)	5	13

Table 105: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis (Including ADEM and Meningoencephalitis)

Case Characteristics		Number of Cases Received During the Reporting Period=127	Number of Cases Received Cumulatively=297
Country/Territory[b]	United States	40	124
	Germany	33	42
	Brazil	7	10
	Czech Republic	4	5
	France	4	6
	Belgium	3	5
	Estonia	3	3
	Korea, Republic of	3	24
	Netherlands	3	26
	South Africa	3	7
	Ireland	2	2
	Latvia	2	2
	Luxembourg	2	2
	Spain	2	4
Event Characteristics		**Number of Events=132**	**Number of Events=309**
Seriousness (Event Level)[c]	Serious	95	216
	Nonserious	37	93
Outcome (Event Level)[c]	Not resolved	44	103
	Resolved	28	71
	Resolving	27	47
	Resolved with sequelae	2	4
	Fatal	5	12
	NR	26	72

Key: ADEM=Acute Disseminated Encephalomyelitis; NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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 reporting encephalitis (including ADEM and meningoencephalitis) with the use of Ad26.COV2.S is presented in Table 106 below. A single case may contain more than 1 EOI.

Table 106: Frequency of MedDRA PTs in Cases Reporting Encephalitis (Including ADEM and Meningoencephalitis) With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Photophobia	11	37	27	93
Delirium	26	0	47	0
Encephalitis	14	0	41	0
Encephalopathy	10	0	20	0

Key: ADEM=Acute Disseminated Encephalomyelitis; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

a: The MedDRA PTs of interest with frequency ≥10 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 4 cases reporting encephalitis (including ADEM and meningoencephalitis) were retrieved from Janssen Sponsored Clinical Studies. All 4 cases were from VAC31518COV3001. These 4 cases each reported 1 serious EOI. Of these 4 cases, the most frequently reported country/territory of origin was South Africa (n=2) followed by Brazil (n=1) ,and the US (n=1). Of these 4 cases, 2 concerned females and 2 males. The age range was 22 to 80 years.

The EOI included hepatic encephalopathy, metabolic encephalopathy, meningitis, and delirium (n=1 each). All 4 cases were determined not to be cases of encephalitis (BC Level 5). The mean and median TTO were 344 days each. Where reported (n=4), the outcomes were not resolved and resolving (n=2 each). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=4).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting encephalitis (including ADEM and meningoencephalitis) was retrieved from a Janssen Supported Clinical Study. The case was from VAC31518COV3021 and concerned a 42-year-old female from [redacted] who experienced a serious EOI of meningitis aseptic. This case lacked sufficient evidence to meet any BC case definition level and was assessed as BC Level 4. The TTO was 4 days after booster dose vaccination, and the outcome was reported as resolving. The Company and Sponsor's causality assessment of the EOI was reported as related.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 122 cases reporting encephalitis (including ADEM and meningoencephalitis) were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 122 cases reported 90 serious EOI. Of these 122 cases, the most frequently reported country/territory of origin was the US (n=39)

followed by Germany (n=33). Of the 122 cases, 69 concerned females, 49 males, and 4 had no sex reported. The age range was 17 to 98 years.

The EOI included photophobia (n=48), delirium (n=25), encephalitis (n=14), and encephalopathy (n=10). All cases with EOI encephalitis (n=14) lacked sufficient evidence to meet any BC case definition level and were assessed as BC Level 4. The reported mean and median TTO was 37 days and 1 day, respectively. Where reported (n=101), the outcomes were not resolved (n=42), resolved (n=27), resolving (n=25), fatal (n=5), and resolved with sequelae (n=2). The EOI with a fatal outcome were encephalopathy (n=3), followed by metabolic encephalopathy and encephalitis (n=1 each). The case reporting EOI of encephalitis with a fatal outcome was assessed as BC Level 4.

Additionally, 3 ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information about encephalitis (including ADEM and meningoencephalitis).

Fatal Cases

A total of 5 cases (4 medically confirmed and 1 medically unconfirmed) were received during the reporting period, with each containing an EOI of fatal outcome. These cases concerned 2 females and 3 males with an age range from 44 to 94 years. When reported (n=4), TTO in these cases ranged from 8 to 298 days post-vaccination. The most frequently reported EOI was encephalopathy (n=3), followed by metabolic encephalopathy and encephalitis (n=1 each). One case reported encephalitis but lacked sufficient evidence to meet any BC case definition level (BC Level 4), and the remaining 4 were determined not to be cases of encephalitis (BC Level 5).

Two out of 5 cases did not meet the risk window of 42 days, with TTO reported as 170 and 298 days, respectively. In both cases there were other factors more likely to be associated with the EOI, such as COVID-19 infection and septic shock.

The remaining 3 cases reported TTO within the risk window of 1 to 42 days. One of these cases concerned a 64-year-old female with no past medical history, concurrent conditions, or concomitant medications reported. The patient experienced encephalitis in the context of multiple organ failure and cavernous sinus thrombosis and died 11 days post-vaccination. The immediate cause of death was listed as multi-organ system failure, and it is unknown if an autopsy was performed. The workup for alternative aetiologies is limited in scope for this case; thus, a causal relationship of encephalitis to vaccination cannot be excluded.

Another case concerned a 44-year-old with encephalopathy and renal failure that occurred on an unspecified day post-vaccination. The case lacks essential information on medical history, concomitant medication, clinical course of events, diagnostic workup/laboratory results, autopsy result, and TTO precluding meaningful medical assessment.

The last case concerned a 51-year-old female who experienced encephalopathy 18 days

post-vaccination, which was reported along with multiple organ dysfunction syndrome, and concurrent acute kidney injury with anuria. The cause of death was attributed to significant pulmonary haemorrhage, but it is unknown if an autopsy was performed. The patient had significant underlying conditions and was polymedicated, which likely contributed to the events and the fatal outcome. Therefore, the causality of the Ad26.COV2.S vaccine was unlikely in this case.

Booster Dose

Cumulatively, 8 serious (4 medically confirmed and 4 medically unconfirmed) cases were identified reporting encephalitis (including ADEM and meningoencephalitis) in individuals who received the booster dose. Of these cases, 4 were heterologous, and 4 were homologous. CIOMS II LL is presented in Appendix 7.24.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 107.

Table 107: Encephalitis (Incl. ADEM) w/o Photophobia, ADEM: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad 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 (incl. ADEM) *w/o Photophobia*	**US**	18 to 59	34.60	0.287	(0.199, 0.399)	4.969	(3.453, 6.924)
		≥60	17.35	0.204	(0.119, 0.325)	3.177	(1.862, 5.063)
	EU	18 to 59	46.84	0.339	(0.249, 0.452)	5.883	(4.320, 7.827)
		≥60	8.15	0.115	(0.050, 0.225)	1.790	(0.780, 3.506)
ADEM	**US**	18 to 59	7.65	0.634	(0.267, 1.267)	3.296	(1.390, 6.590)
		≥60	0.34	0.208	(0.000, 2.668)	1.038	(0.000, 13.341)
	EU	18 to 59	3.00	0.217	(0.045, 0.635)	1.130	(0.233, 3.304)
		≥60	0.00	0.000	(0.000, 2.700)	0.000	(0.000, 13.502)

Key: ADEM=Acute Disseminated Encephalomyelitis; AESI=Adverse Event Special Interest; CI=Confidence Interval; EOI=Event of Interest; EU=European Union; Incl.=Including; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States; W/O=Without

a: Counts included EOI (from valid/invalid cases) that occurred within the risk window (day: 1 to 42), and where time-to-onset was day 0 or not reported.

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

Encephalitis (incl. ADEM) without Photophobia

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU across both age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US and EU for both age groups.

ADEM

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage

and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU across both age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US for both age group. In the EU, the O/E ratio was >1 in the 18 to 59 age group only.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was >1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the risk window (day: 1 to 42) only.

Results of the restricted O/E and sensitivity analysis are presented in Table 108.

Table 108: Encephalitis (Incl. ADEM) w/o Photophobia, ADEM: Restricted O/E Analysis With Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
AESI	**Region**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
Encephalitis (incl. ADEM) *w/o Photophobia*	**US**	18 to 59	21.95	0.182	(0.114, 0.275)	3.152	(1.974, 4.775)
		≥60	13.01	0.153	(0.081, 0.261)	2.382	(1.269, 4.073)
	EU	18 to 59	24.00	0.174	(0.111, 0.259)	3.014	(1.931, 4.485)
		≥60	5.00	0.070	(0.023, 0.164)	1.098	(0.357, 2.562)
ADEM	**US**	18 to 59	7.65	0.634	(0.267, 1.267)	3.296	(1.390, 6.590)
		≥60	0.34	0.208	(0.000, 2.668)	1.038	(0.000, 13.341)
	EU	18 to 59	2.00	0.145	(0.018, 0.524)	0.754	(0.091, 2.722)

Key: ADEM=Acute Disseminated Encephalomyelitis; AESI=Adverse Event Special Interest; CI=Confidence Interval; EOI=Event of Interest; EU=European Union; Incl.=Including; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States; W/O=Without

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

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

Encephalitis (incl. ADEM) without Photophobia

A review of the results for the US and EU restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU across both age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US and EU for both age groups.

ADEM

A review of the results for the US restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU for all concerned age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US for both age groups. In the EU, the O/E ratio was <1 for the 18 to 59 age group.

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

Conclusion

During the reporting period, a cumulative review of encephalitis (including acute disseminated encephalomyelitis) was conducted by the Company and presented in the Monthly SSR covering the month of September 2021. The Company considered there is insufficient evidence to conclude a clear causal association between encephalitis (including ADEM) and Ad26.COV2.S, based on a lack of established biological plausibility, no observed numerical imbalance between vaccine and placebo from 2 large Phase 3 double-blinded trials, as well as the O/E analysis showing no imbalance compared to the general population.

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 current reporting period and cumulatively, and an O/E analysis, no new safety information was identified during the reporting period for encephalitis (including ADEM and meningoencephalitis). The Company will continue to closely monitor cases of encephalitis (including ADEM) as an AESI.

16.3.6.4.4. Multiple Sclerosis (Including Optic Neuritis)

Introduction

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

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 90), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 31 (11 medically confirmed and 20 medically unconfirmed) cases reporting multiple sclerosis (including optic neuritis) were identified. All 31 cases were serious and reported a total of 32 serious events.

All 31 cases were reported from Post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 57 (29 medically confirmed and 28 medically unconfirmed) cases reporting multiple sclerosis (including optic neuritis) were identified. All 57 cases were serious and reported a total of 59 serious events.

Of these 57 cumulative cases received, 1 was reported from a Janssen Sponsored Clinical Study, 1 from a Janssen Supported Clinical Study, and 55 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 109 below.

Table 109: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis (Including Optic Neuritis)

Case Characteristics		Number of Cases Received During the Reporting Period=31	Number of Cases Received Cumulatively=57
Sex	Female	15	34
	Male	14	21
	NR	2	2
Age (Years)[a]	18 to 35	8	15
Minimum:19	36 to 50	14	24
Maximum:73	51 to 64	4	11
Mean:42	≥65	1	2
Median:40	NR	4	5
Source	Spontaneous	30	54
	Clinical study (non-interventional; solicited)	1	1
	Clinical study (interventional; non-solicited)	0	2
Country/Territory[b]	United States	12	35
	Germany	5	5
	Greece	3	3
	Italy	2	2
	Belgium	1	1
	Czech Republic	1	1
	France	1	1
	Ireland	1	1
	Mexico	1	1
	Netherlands	1	1
	Philippines	1	1
	Portugal	1	1

Table 109: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis (Including Optic Neuritis)

Case Characteristics		Number of Cases Received During the Reporting Period=31	Number of Cases Received Cumulatively=57
	Spain	1	1
Event Characteristics		**Number of Events=32**	**Number of Events=59**
Seriousness (Event Level)[c]	Serious	32	59
Outcome (Event Level)[c]	Not resolved	19	41
	Resolved	4	4
	Resolved with sequelae	3	4
	Resolving	2	4
	NR	4	6

Key: NR=Not Reported.
a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).
b: Countries/Territories are listed in descending order for the current reporting period (25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

The frequency distribution of the MedDRA PTs of interest reported in cases reporting multiple sclerosis (including optic neuritis) with the use of Ad26.COV2.S is presented in Table 110 below. A single case may contain more than 1 EOI.

Table 110: Frequency of MedDRA PTs in Cases Reporting Multiple Sclerosis (Including Optic Neuritis) With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Optic neuritis	15	0	24	0
Multiple sclerosis	13	0	28	0
Multiple sclerosis relapse	4	0	6	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by descending order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 31 cases reporting multiple sclerosis (including optic neuritis) were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 31 cases reported 32 serious EOI. Of these 31 cases, the most frequently reported country/territory of origin was the US (n=12) followed by Germany (n=5), and Greece (n=3). Of the 31 cases, 15 concerned females, 14 males, and 2 had no sex reported. The age range was 19 to 73 years.

The EOI reported were optic neuritis (n=15), multiple sclerosis (n=13), and multiple sclerosis relapse (n=4). The reported mean and median TTO was 34.6 days and 14.5 days, respectively. Where reported (n=28), the outcomes were not resolved (n=19), resolved (n=4), resolved with sequelae (n=3), and resolving (n=2). There were no fatal cases received during the reporting period.

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed and 1 case concerned a 19-year-old female who experienced left eye pain a week after receiving Ad26.COV2.S and subsequent amaurosis and left vision loss. The patient was diagnosed with inflammatory optic neuritis on an unspecified date. The authors stated that the causality could not be confirmed due to lack of a biomarker and suggested further research into a potential pathogenic mechanism.

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 multiple sclerosis (including optic neuritis) being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, no cases were identified reporting multiple sclerosis (including optic neuritis) in individuals who received the booster dose.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 111.

Table 111: Multiple Sclerosis (Including Optic Neuritis): Broad O/E Analysis With Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	30.25	0.119	(0.080, 0.170)	0.238	(0.161, 0.339)
	≥60	3.69	0.041	(0.010, 0.108)	0.081	(0.021, 0.215)
EU	18 to 59	16.92	0.040	(0.023, 0.065)	0.294	(0.171, 0.472)
	≥60	1.07	0.010	(0.000, 0.052)	0.072	(0.002, 0.382)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 90), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Conclusion

Based on the review of the literature (ie., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new critical safety information was identified during the reporting period for multiple sclerosis (including optic neuritis). The Company will continue to closely monitor this event as an AESI.

16.3.6.4.5. Narcolepsy

Introduction

Narcolepsy is listed as an AESI in the cRMP, EU RMP, and 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid

initial and booster ICSRs that occurred within the risk window (day: 1 to 180), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 209 (38 medically confirmed and 171 medically unconfirmed) cases reporting narcolepsy were identified. Of these cases, 83 were serious and 126 nonserious, and reported a total of 209 events (37 serious; 172 nonserious).

All 209 cases were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 462 (66 medically confirmed and 396 medically unconfirmed) cases reporting narcolepsy were identified. Of these cases, 148 were serious and 314 nonserious, and reported a total of 463 events (65 serious; 398 nonserious).

Of these 462 cumulative cases received, 1 was from a Janssen Supported Clinical Study, and 461 from Post-marketing Sources (including spontaneous and solicited cases. No cases were reported from Janssen Sponsored Clinical Studies.

An overview of these cases is presented in Table 112 below.

Table 112: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting Period=209	Number of Cases Received Cumulatively=462
Sex	Female	102	239
	Male	91	175
	NR	16	48
Age (Years)[a]	18 to 35	49	88
Minimum:18	36 to 50	51	91
Maximum:79	51 to 64	59	122
Mean:46.6	≥65	20	65
Median:47	Adult	3	5
	NR	27	91
Source	Spontaneous	197	447
	Clinical study (non-interventional;	12	14

Table 112: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting Period=209	Number of Cases Received Cumulatively=462
	solicited)		
	Clinical study (non-interventional; non-solicited)	0	1
Country/Territory[b]	United States	103	302
	Germany	50	56
	Netherlands	7	14
	Belgium	6	12
	France	5	7
	Poland	4	8
	Austria	3	6
	Brazil	3	9
	Bulgaria	3	3
	Ireland	3	7
	Latvia	3	4
	Spain	3	7
Event Characteristics		**Number of Events=209**	**Number of Events=463**
Seriousness (Event Level)[c]	Nonserious	172	398
	Serious	37	65
Outcome (Event Level)[c]	Not resolved	77	147
	Resolved	48	105
	Resolving	21	35
	Fatal	0	1
	NR	63	175

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting narcolepsy with the use of Ad26.COV2.S is presented in Table 113 below. A single case may report more than 1 EOI.

Table 113: Frequency of MedDRA PTs in Cases Reporting Narcolepsy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	29	104	45	187
Hypersomnia	8	68	17	211

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by descending order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 209 cases reporting narcolepsy were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 209 cases reported 37 serious EOI. Of these 209 cases, the most frequently reported country/territory of origin was the US (n=103) followed by Germany (n=50). Of the 209 cases, 102 concerned females, 91 males, and 16 had no sex reported. The age range was 18 to 79 years.

The EOI included sleep disorder (n=133), and hypersomnia (n=76). The reported mean and median TTO was 17.6 days and 1 day, respectively. Where reported (n=146), the outcomes were not resolved (n=77), resolved (n=48), and resolving (n=21). There was 1 fatal case; however, there was no fatal EOI reported.

There were no ICSR literature cases identified during the reporting period.

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 narcolepsy being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 18 (3 medically confirmed and 15 medically unconfirmed) cases were identified reporting narcolepsy in individuals who received the booster dose. There were 7 serious and 11 nonserious cases. Of these cases, 12 were homologous and 6 were heterologous,. CIOMS II LL

is presented in Appendix 7.25.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 114.

Table 114: Narcolepsy: Broad O/E Analysis With Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	190.80	0.116	(0.100, 0.133)	0.265	(0.229, 0.305)
	≥60	104.31	0.181	(0.148, 0.219)	0.362	(0.296, 0.439)
EU	18 to 59	122.55	1.131	(0.940, 1.350)	4.336	(3.603, 5.176)
	≥60	20.34	2.956	(1.814,4.549)	24.961	(15.318, 38.413)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 180), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of <1 in both age groups. In the EU, the O/E ratio was >1 for both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US showed an O/E ratio of <1 for both age groups. In the EU, the O/E ratio in the sensitivity analysis was >1 for both age groups.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was >1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the risk window (day: 1 to 180). Results of the restricted O/E and sensitivity analysis for narcolepsy are presented in Table 115.

Table 115: Narcolepsy: Restricted O/E Analysis With Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis					Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
EU	18 to 59	57.27	0.529	(0.401, 0.684)	2.026	(1.536, 2.624)
	≥60	13.67	1.987	(1.077, 3.353)	16.776	(9.095, 28.318)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 180) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of >1 in the EU for the ≥60 age group

only. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the EU for both age groups. Since the previous PBRER O/E data-lock point (31 August 2021), the O/E ratio for the EU ≥60 age group increased from <1 to >1 (statistically significant).

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

Conclusion

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

Since launch, no signal for narcolepsy has been observed for Ad26.COV2.S. Most of the cases retrieved were hypersomnia or other sleep disorders not meeting the definition of narcolepsy. Based on this, the Company proposes to monitor these cases through routine pharmacovigilance activities.

16.3.6.4.6. Sensorineural Hearing Loss

Introduction

Sensorineural hearing loss (SNHL) is listed as an AESI in the cRMP, EU RMP, and US PVP.

Tinnitus is listed as a rare adverse reaction following Ad26.COV2.S in the CCDS, EU SmPC, and US Fact Sheet.

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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups 18 to 59 and ≥60, and risk windows of 1 to 14 and 1 to 21 days. Based on available background incidence rates, an analysis was performed separately for SNHL without tinnitus and for tinnitus alone. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window, and where TTO was 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include: exposure calculations, risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 774 (61 medically confirmed and 713 medically unconfirmed) cases reporting SNHL were identified. Of these cases, 196 were serious and 578 nonserious, and reported a total of 829 events (177 serious; 652 nonserious).

Of these 774 cases during the reporting period of 25 August 2021 to 24 February 2022, 1 was reported from a Janssen Supported Clinical Study and 773 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies.

Cumulatively, 1,144 (120 medically confirmed and 1,024 medically unconfirmed) cases reporting SNHL were identified. Of these cases, 322 were serious and 822 nonserious, and reported a total of 1,237 events (268 serious; 969 nonserious).

Of these 1,144 cumulative cases received, 2 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 1,140 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 116 below.

Table 116: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

Case Characteristics		Number of Cases Received During the Reporting Period=774	Number of Cases Received Cumulatively=1,144
Sex	Male	399	515
	Female	346	571
	NR	29	58
Age (Years)[a]	0 to 17	0	1
Minimum:19	18 to 35	143	197
Maximum:98	36 to 50	203	293
Mean:46.7	51 to 64	253	373
Median:49	≥65	47	85
	Adult	69	74
	Elderly	2	3
	NR	57	118
Source	Spontaneous	751	1,105
	Clinical study (non-interventional; solicited)	22	35
	Clinical study (non-interventional; non-solicited)	1	1
	Clinical study (interventional; non-solicited)	0	3
Country/Territory[b]	Netherlands	283	356
	Germany	172	179

Table 116: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

Case Characteristics		Number of Cases Received During the Reporting Period=774	Number of Cases Received Cumulatively=1,144
	United States	112	318
	France	23	30
	Austria	21	23
	Belgium	20	37
	Italy	18	29
	Portugal	17	21
	Ireland	15	18
	Czech Republic	14	14
	Croatia	13	15
	Brazil	11	20
Event Characteristics		**Number of Events=829**	**Number of Events=1,237**
Seriousness (Event Level)[c]	Nonserious	652	969
	Serious	177	268
Outcome (Event Level)[c]	Not resolved	519	739
	Resolved	102	157
	Resolving	84	143
	Resolved with sequelae	27	30
	Fatal	1	1
	NR	96	167

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency >10 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting SNHL with the use of Ad26.COV2.S is presented in Table 117 below. A single case may contain more than 1 EOI.

Table 117: Frequency of MedDRA PTs in Cases Reporting Sensorineural Hearing Loss With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Tinnitus	101	624	133	912
Hypoacusis	21	25	29	52
Deafness	30	0	56	0
Deafness unilateral	13	0	21	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest with frequency >10 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting SNHL was retrieved from Janssen Supported Clinical Studies. The case was from VAC31518COV4007 and concerned a 54-year-old female from [redacted] who experienced a nonserious EOI of tinnitus. The TTO and outcome were not reported. The Company and Sponsor's causality assessment of the EOI was reported as not related.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 773 cases reporting SNHL were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 773 cases reported 177 serious EOI. Of these 773 cases, the most frequently reported country/territory of origin was the Netherlands (n=283) followed by Germany (n=172), and the US (n=112). Of the 773 cases, 399 concerned males, 345 females, and 29 had no sex reported. The age range was 19 to 98 years.

The EOI (n≥30) included tinnitus (n=724), hypoacusis (n=46), and deafness (n=30). The reported mean and median TTO was 14.6 days and 2 days, respectively. Where reported (n=733), the outcomes were not resolved (n=519), resolved (n=102), resolving (n=84), resolved with sequelae (n=27), and fatal (n=1). The EOI with a fatal outcome was tinnitus.

The majority of cases (n=671) reported isolated tinnitus. The event mostly occurred in the context of systemic reactogenicity and no diagnostic test results consistent with SNHL were provided in these cases. Overall, limited information on the clinical course of the events was available.

In the remaining 102 cases, the reported events referred to bi-or unilateral deafness and/or deafness

neurosensory, transitory deafness, hypoacusis, sudden hearing loss, and auditory disorder (with or without tinnitus). Most cases presented limited information for a meaningful medical assessment. Four cases specifically reported that the patient experienced SNHL. In 1 case, the EOI was outside the 60-day risk window. Two cases were missing audiogram results confirming the SNHL and were confounded by the patient's pre-existing hearing disorder in 1 case, and TIA with aggravation of underlying hypertension in the other. The last case concerned a 54-year-old female who experienced SNHL 1 day post-vaccination. Audiogram result was consistent with SNHL; however, the details of the audiogram with the degree of hearing loss and frequencies affected was not reported. The case presented limited information on the clinical course and full otologic workup; however, considering the short TTO causality with the vaccine cannot be excluded.

No ICSR literature cases were retrieved from the search strategy during the reporting period.

Fatal Cases

There was 1 fatal case reported, which concerned a 21-year-old male who 25 days post-vaccination experienced status epilepticus and ischaemic stroke with initial symptoms including tinnitus. Notable antibody P4F test was negative. Cause of death was reported as unknown. In this case, the event of tinnitus was likely only a symptom of the underlying medical event and not directly caused by the vaccine. This case is also discussed in Section 16.3.6.5.1, Cerebrovascular Events.

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 SNHL being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 22 (3 medically confirmed and 19 medically unconfirmed) cases were identified reporting SNHL in individuals who received the booster dose. There were 7 serious and 15 nonserious cases. Of these cases, 16 were homologous, and 6 were heterologous. CIOMS II LL is presented in Appendix 7.26.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 118.

Table 118: Sensorineural Hearing Loss Without Tinnitus, Tinnitus: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

		Broad O/E Analysis				Sensitivity Analysis	
AESI/PT	**Region (Risk Window, Days)**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
Sensorineural Hearing Loss *w/o tinnitus*	US (1-21)	18 to 59	44.01	0.191	(0.139, 0.257)	0.941	(0.684, 1.263)
		≥60	19.75	0.103	(0.063, 0.160)	0.206	(0.126, 0.319)
	US (1-14)	18 to 59	41.01	0.267	(0.192, 0.362)	1.312	(0.942, 1.780)
		≥60	16.75	0.131	(0.076, 0.211)	0.262	(0.152, 0.421)
- Tinnitus	US (1-21)	18 to 59	170.50	0.057	(0.049, 0.066)	0.301	(0.258, 0.350)
		≥60	87.63	0.047	(0.038, 0.058)	0.334	(0.268, 0.411)
	US (1-14)	18 to 59	165.50	0.083	(0.071, 0.096)	0.438	(0.374, 0.510)
		≥60	83.63	0.067	(0.053, 0.083)	0.477	(0.380, 0.591)
Sensorineural Hearing Loss *w/o tinnitus*	EU (1-21)	18 to 59	63.60	0.242	(0.186, 0.310)	1.192	(0.917, 1.523)
		≥60	19.37	0.121	(0.073, 0.188)	0.242	(0.147, 0.376)
	EU (1-14)	18 to 59	58.68	0.335	(0.255, 0.432)	1.647	(1.253, 2.126)
		≥60	18.30	0.171	(0.102, 0.270)	0.343	(0.204, 0.540)
- Tinnitus	EU (1-21)	18 to 59	538.04	0.157	(0.144, 0.171)	0.834	(0.765, 0.907)
		≥60	56.53	0.036	(0.027, 0.047)	0.258	(0.195, 0.334)
	EU (1-14)	18 to 59	514.36	0.225	(0.206, 0.246)	1.194	(1.093, 1.302)
		≥60	51.23	0.049	(0.037, 0.064)	0.350	(0.261, 0.460)

Key: AESI=Adverse Event of Special Interest; CI=Confidence Interval; EOI=Event of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; PT=Preferred Term; RP=Reporting Percentage; US=United States; W/O=Without

a: Counts included EOI (from valid/invalid cases) that occurred within the risk window (day: 1 to 21, 1 to 14), and where time-to-onset was day 0 or not reported.

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

*: Tinnitus is not an AESI but falls under the subcategory of AESI: Sensorineural Hearing Loss.

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) for both SNHL without tinnitus and tinnitus alone showed an O/E ratio of <1 in both the US and EU for both risk windows (1 to 21, 1 to 14 days) and both age groups. The sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 for SNHL without tinnitus in the US (risk window: 1 to 14 days) 18 to 59 age group only. In the EU, the sensitivity analysis O/E ratio was >1 in the 18 to 59 age group only for SNHL without tinnitus (risk windows: 1 to 21, 1 to 14 days) and for the tinnitus alone (risk window: 1 to 14 days) 18 to 59 age group.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was >1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the risk window (day: 1 to 14, 1 to 21) only. A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was >1 in the broad sensitivity analysis (see Table 119).

Table 119: Sensorineural Hearing Loss Without Tinnitus, Tinnitus: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Restricted O/E Analysis					Sensitivity Analysis	
AESI/PT	**Region (Risk Window, Days)**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
Sensorineural Hearing Loss *w/o tinnitus*	US (1-14)	18 to 59	19.55	0.127	(0.077, 0.197)	0.626	(0.380, 0.971)
Sensorineural Hearing Loss *w/o tinnitus*	EU (1-21)	18 to 59	32.67	0.125	(0.086, 0.175)	0.612	(0.421, 0.861)
	EU (1-14)	18 to 59	27.84	0.159	(0.105, 0.230)	0.781	(0.519, 1.131)
- Tinnitus	EU (1-14)	18 to 59	302.70	0.133	(0.118, 0.148)	0.703	(0.626, 0.786)

Key: AESI=Adverse Event of Special Interest; CI=Confidence Interval; EOI=Event of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; PT=Preferred Term; RP=Reporting Percentage; US=United States; W/O=Without

a: Counts included EOI (from valid/invalid cases) that occurred within the risk window (Day: 1 to 21, 1 to 14) only.

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

*: Tinnitus is not an AESI but falls under the subcategory of AESI: Sensorineural Hearing Loss.

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US and EU an O/E ratio of <1 for all risk windows and age groups concerned. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) also showed for the US and EU an O/E ratio of <1 for all risk windows and age groups concerned.

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

Conclusion

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

The Company has included tinnitus as a rare ADR in the CCDS, EU SmPC, and US Fact Sheets following the imbalance observed both in clinical trials as well as in the post-marketing settings. Analysis of pure tinnitus cases suggest these events are likely result of systemic reactogenicity, as most have a very close temporal association to the vaccination event and are mild and transient in nature. In cases where tinnitus has been associated with SNHL, other terms are usually included by the reporter. Based on these findings, the Company proposes to take the PT "Tinnitus" from the search strategy for SNHL.

16.3.6.4.7. Transverse Myelitis

Introduction

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

On 23 September 2021, a signal was identified for transverse myelitis and encephalitis (including acute disseminated encephalomyelitis) with the use of COVID-19 vaccine AD26.COV2.S based on the EMA PRAC Assessment Report for the August 2021 Monthly SSR. The evaluation method included a cumulative case series review of available data in the Company global safety database through 31 August 2021 and was presented within the previous PBRER. Additional information can be found within the current PBRER in Section 16.2.1.1.3.

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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 42), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations [for initial and booster doses], risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 49 (29 medically confirmed and 20 medically unconfirmed) cases reporting transverse myelitis were identified. All 49 cases were serious and reported a total of 54 serious events.

Of these 49 cases during the reporting period of 25 August 2021 to 24 February 2022, 1 was reported from a Janssen Sponsored Clinical Study and 48 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 94 cases (65 medically confirmed and 29 medically unconfirmed) reporting transverse myelitis were identified. All 94 cases were serious and reported a total of 109 serious events.

Of these 94 cumulative cases received, 1 was reported from a Janssen Sponsored Clinical Study, 2 from Janssen Supported Clinical Studies, and 91 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 120 below.

Table 120: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Transverse Myelitis

Case Characteristics		Number of Cases Received During the Reporting Period=49	Number of Cases Received Cumulatively=94
Sex	Male	31	54
	Female	15	37
	NR	3	3
Age (Years)[a]	18 to 35	9	24
Minimum:18	36 to 50	20	33
Maximum:68	51 to 64	11	25
Mean:44.8	≥65	3	5
Median:43	Adult	0	1
	NR	6	6
Source	Spontaneous	48	91
	Clinical study (interventional; non-solicited)	1	3
Country/Territory[b]	United States	23	53
	Germany	10	15
	Italy	3	3
	Brazil	2	5
	France	2	2
	Netherlands	2	6
	Ireland	1	1
	Mexico	1	1
	Morocco	1	1
	Portugal	1	1
	Romania	1	1
	South Africa	1	3
	United Kingdom	1	1
Event Characteristics		**Number of Events=54**	**Number of Events=109**
Seriousness (Event Level)[c]	Serious	54	109
Outcome (Event Level)[c]	Not resolved	25	61
	Resolving	11	20
	Resolved	1	3
	Resolved with sequelae	1	1
	NR	16	24

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in descending order for the current reporting period (25 August 2021 to 24 February 2022).

Table 120: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Transverse Myelitis

Case Characteristics	Number of Cases Received During the Reporting Period=49	Number of Cases Received Cumulatively=94

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting transverse myelitis with the use of Ad26.COV2.S is presented in Table 121 below. A single case may contain more than 1 EOI.

Table 121: Frequency of MedDRA PTs in Cases Reporting Transverse Myelitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myelitis transverse	27	0	57	0
Demyelination	15	0	25	0
Myelitis	11	0	20	0
Neuromyelitis optica spectrum disorder	1	0	5	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by descending order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 1 case reporting transverse myelitis was retrieved from a Janssen Sponsored Clinical study. The case was from VAC31518COV3009 and concerned a 63-year-old female from the [redacted] who experienced a serious EOI of transverse myelitis. The TTO was not reported, and the outcome was reported as resolving. The Sponsor and Investigator's causality assessments of the EOI were both reported as not related (n=1).

Janssen Supported Clinical Studies

There were no cases retrieved from search of the Company Global Safety Database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 48 cases reporting transverse

myelitis were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 48 cases reported 53 serious EOI. Of these 48 cases, the most frequently reported country/territory of origin was the US (n=23) followed by Germany (n=10). These 48 cases concerned 31 males, 14 females, and 3 with no sex reported. The age range was 18 to 68 years.

The EOI included myelitis transverse (n=26), demyelination (n=15), myelitis (n=11), and neuromyelitis optica spectrum disorder (n=1). BC Level assessment for these cases was as follows: BC Level 2 (n=2), BC Level 3 (n=4), BC Level 4 (n=35) and BC Level 5 (n=7). The reported mean and median TTO was 25.6 days and 18 days, respectively. Where reported (n=37), the outcomes were not resolved (n=25), resolving (n=10), and resolved and resolved with sequelae (n=1 each). There were no cases with a fatal outcome received during the reporting period for this AESI.

Additionally, 2 ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information on transverse myelitis.

Booster Dose

Cumulatively, no cases were identified reporting transverse myelitis in individuals who received the booster dose.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 122.

Table 122: Transverse Myelitis: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	41.25	2.666	(1.915, 3.613)	5.332	(3.830, 7.227)
	≥60	8.69	1.591	(0.716, 3.054)	3.183	(1.431, 6.108)
EU	18 to 59	21.84	2.939	(1.838, 4.456)	20.574	(12.869, 31.195)
	≥60	4.15	11.392	(3.202, 28.709)	60.759	(17.078, 153.117)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of >1 for both the US and EU across both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower

bound background incidence rate) again showed an O/E ratio of >1 in the EU and US, for both age groups.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was > 1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the risk window (day: 1 to 42) only. Results of the broad O/E and sensitivity analysis for transverse myelitis are presented in Table 123.

Table 123: Restricted O/E Analysis Results–Transverse Myelitis (Cumulative to 24 February 2022)

	Restricted O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	33.00	2.133	(1.468, 2.995)	4.265	(2.936, 5.990)
	≥60	6.00	1.099	(0.403, 2.392)	2.197	(0.806, 4.783)
EU	18 to 59	16.92	2.277	(1.325, 3.650)	15.939	(9.272, 25.548)
	≥60	2.07	5.682	(0.726, 20.137)	30.306	(3.871, 107.398)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 42) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) again showed an O/E ratio of >1 in the EU and US, for both age groups.

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

Conclusion

During the reporting period, a cumulative review of transverse myelitis was conducted by the Company and presented in the Monthly SSR covering the month of September 2021. The Company considered there is insufficient evidence to conclude a clear causal association between transverse myelitis and Ad26.COV2.S, based on a lack of established biological plausibility, no observed numerical imbalance between vaccine and placebo from 2 large Phase 3 double-blinded trials, as well as the O/E analysis showing no imbalance compared to the general population.

However, in the final AR for this Monthly SSR, the EMA PRAC Rapporteur disagreed with the Company's assessment, considering a number of well-documented cases meeting BC's criteria of level 2 and 3 of diagnostic certainty occurring in close temporal relationship to vaccination with no other evident explanatory factors. The EU Prescribing Information (PI) has been amended accordingly to reflect the decision from PRAC. Similar amendments have been made to the local PI during the reporting period for Bahrain, Brazil, Canada, EU, France, Kingdom of Saudi Arabia,

Kuwait, Oman, Qatar, South Africa, and the United Arab Emirate. The Company still considers there is insufficient evidence for a causal association between Ad26.COV2.S and transverse myelitis.

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.

16.3.6.5. Vascular Disorders

16.3.6.5.1. Cerebrovascular Events

Introduction

Cerebrovascular events are included in the list of AESIs as described in the cRMP, EU RMP, and 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.

A broad and restricted O/E analysis was performed for both cerebrovascular-haemorrhagic and non-haemorrhagic events in the US and EU, stratified by sex (female, male) and age groups: 18 to 29, 30 to 39, 40 to 49, 50 to 64, 65 to 74 and ≥75. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 28). The broad analysis included EOI cases that occurred within the risk window and cases where the TTO was day 0 or not reported. Results of the broad analysis are available in Appendix 6.2. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted O/E analysis with sensitivity analysis was performed. This included EOI that were known to have occurred within the risk window only (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 607 (315 medically confirmed and 292 medically unconfirmed) cases reporting cerebrovascular events were identified. Of these cases, 599 were serious and 8 nonserious, and reported a total of 789 events (781 serious; 8 nonserious).

Of these 607 cases during the reporting period of 25 August 2021 to 24 February 2022, 59 were reported from Janssen Sponsored Clinical Studies and 548 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported

Clinical Studies.

Cumulatively, 1,520 (919 medically confirmed and 601 medically unconfirmed) cases reporting cerebrovascular events were identified. Of these cases, 1,510 were serious and 10 nonserious, and reported a total of 2,051 events (2,038 serious; 13 nonserious).

Of these 1,520 cumulative cases received, 105 were reported from Janssen Sponsored Clinical Studies, 17 from Janssen Supported Clinical Studies, and 1,398 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 124 below.

Table 124: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Period=607	Number of Cases Received Cumulatively=1,520
Sex	Male	304	682
	Female	271	790
	NR	32	48
Age (Years)[a]	0 to 17	2	3
Minimum:17	18 to 35	59	163
Maximum:99	36 to 50	131	338
Mean:55	51 to 64	184	461
Median:55	≥65	139	402
	Adult	2	5
	Elderly	1	2
	Neonate	1	1
	NR	88	145
Source	Spontaneous	546	1,392
	Clinical study (interventional; non-solicited)	59	121
	Clinical study (non-interventional; solicited)	2	6
	Clinical study (non-interventional; non-solicited)	0	1
Country/Territory[b]	United States	344	1,059
	Germany	88	120
	Netherlands	21	42
	France	20	39
	Italy	16	39
	Philippines	16	20
	Brazil	12	22
	South Africa	11	38

Table 124: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Period=607	Number of Cases Received Cumulatively=1,520
Event Characteristics		**Number of Events=789**	**Number of Events=2,051**
Seriousness (Event Level)[c]	Serious	781	2,038
	Nonserious	8	13
Outcome (Event Level)[c]	Not resolved	237	764
	Resolved	112	304
	Resolving	92	208
	Fatal	88	203
	Resolved with sequelae	32	50
	NR	228	522

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency >10 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting cerebrovascular events with the use of Ad26.COV2.S is presented in Table 125 below. A single case may contain more than 1 EOI.

Table 125: Frequency of MedDRA PTs in Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cerebrovascular accident	274	0	644	1
Transient ischaemic attack	47	6	138	7
Hemiparesis	49	0	163	0
Cerebral infarction	44	0	91	0
Ischaemic stroke	44	0	111	0
Cerebral venous sinus thrombosis	41	0	127	0

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

a: The MedDRA PTs of interest with frequency >40 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 59 cases reporting cerebrovascular events were retrieved from Janssen Sponsored Clinical Studies. Thirty-nine cases were from VAC31518COV3001, 18 from VAC31518COV3009, 1 from VAC31518COV2008, and 1 from VAC31518COV3003. These 59 cases reported a total of 61 EOI (54 serious; 7 nonserious). Of these 59 cases, the most frequently reported country/territory of origin was the US (n=28) followed by South Africa (n=7), and Brazil (n=6). Of these 59 cases, 37 concerned males and 22 females. The age range was 35 to 87 years.

The EOI (n≥4) included cerebrovascular accident (n=27), transient ischaemic attack (n=13), and ischaemic stroke (n=4). The mean and median TTO was 253 days and 262 days, respectively. The outcome of the 58 EOI was reported as resolved (n=27), resolving (n=15), resolved with sequelae (n=11), and fatal (n=5). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=58), and related (n=1).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 548 cases reporting cerebrovascular events were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 548 cases reported 727 serious EOI. Of these 513 cases, the most frequently reported country of origin was the US (n=316) followed by Germany (n=87), and the Netherlands (n=21). Of the 548 cases, 267 concerned males, 249 females, and 32 had no sex reported. The age range was 17 to 99 years.

The EOI (n>40) included cerebrovascular accident (n=247), hemiparesis (n=47), and cerebral infarction (n=43). The reported mean and median TTO was 61 days and 22 days, respectively. Where reported (n=503), the outcomes were not resolved (n=237), resolved (n=85), resolving (n=77), fatal (n=83), and resolved with sequelae (n=21). The most frequently reported events with a fatal outcome were cerebrovascular accident (n=23), cerebral haemorrhage (n=11), and cerebral venous sinus thrombosis (n=10).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information of cerebrovascular events.

Fatal Cases

Of the 54 fatal cases, 45 occurred in patients ≥41 years of age and 9 occurred in patients ≤40 years

of age. The 9 cases are presented in detail in Table 126 below. Of the remaining 45 cases, the EOI was outside the 28-day risk window in 15 cases. Of the remaining 30 cases, 6 were confounded by the patients' medical history and/or concurrent diseases. Of the remaining 24 cases, 18 lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. In the remaining 6 cases, the information that was provided precluded meaningful medical assessments. Case information for the 45 fatal cases that occurred in patients ≥ 41 years of age are included in Appendix 7.27.1.

Table 126: Summary of Cases Reporting Fatal Cerebrovascular Events in Patients ≤40 Years of Age (n=9)

AER Number Country/Territory Age (Years) Sex	Event(s) of Interest	Medical History/ Concurrent Condition	Concomitant Medications	Summary
20210902066 Germany 34 Male	Cerebral venous sinus thrombosis	Electronic cigarette user	NR	This case (EMEA EVHUMAN NLP, DE-PEI-202100104165) concerned a 34-year-old male who experienced fatal CVST 14 days post-vaccination with Ad26.COV2.S. At an unspecified time after vaccination, the patient experienced headache, vomiting and fever. The patient was hospitalised and subsequently died from vaccine-induced immune thrombocytopenic thrombocytopenia and sinus vein thrombosis. The physician's report from the hospital stated that the findings were typical of a SARS-CoV2 vaccine-induced immune thrombotic thrombocytopenia. **MAH Comment:** Based on evolving knowledge of TTS, per definition from BC, the low platelet count and temporal relationship to vaccination, the events are assessed to have a plausible relationship with vaccination.
20210908182 US 21 Male	Cerebellar stroke Thalamic infarction Cerebral infarction Ischaemic stroke	Anxiety Attention deficit hyperactivity disorder	NR	This case (VAERS ID 1636967) concerned a 21-year-old male who experienced seizure-like activity, aspiration, cerebellar stroke, thalamic infarction, cerebral infarction, hydrocephalus, and posterior fossa syndrome on 25 days post-vaccination with Ad26.COV2.S. The patient was admitted to ED in an intubated condition for treatment of status epilepticus due to seizure-like activity preceded by dizziness, dysarthria, and tinnitus. MRI brain showed bilateral cerebellar and thalamic arterial ischemic stroke with possible basilar occlusion. Coronary CTA and perfusion brain scan were abnormal, and CT of head showed infarcts throughout the cerebellum, pons and brainstem and both posterior cerebral artery territories including the bilateral thalami, early developing lateral and third ventricular hydrocephalus, marked effacement of the basilar cistern, paranasal sinus disease. Platelet count was normal and PF4 antibody test was negative. Patient died due to an unknown cause. **MAH Comment:** Considering the compatible temporal association post-vaccination, the events were assessed to have a plausible relationship with vaccination.

Table 126: Summary of Cases Reporting Fatal Cerebrovascular Events in Patients ≤40 Years of Age (n=9)

AER Number Country/Territory Age (Years) Sex	Event(s) of Interest	Medical History/ Concurrent Condition	Concomitant Medications	Summary
20210959243 Slovenia 20 Female	Cerebral venous sinus thrombosis Cerebral haemorrhage Cerebrovascular accident	Haematuria Thrombocytopenia Tobacco user Loss of consciousness Drug hypersensitivity Dermatitis (Past) Eczema (Past) Dysmenorrhoea (Past)	NR	This case (received from social media post, various news articles and ARSZMP Ministry of Health Slovenia) concerned a 20-year-old female who experienced a fatal CVST with cerebral hemorrhage, cerebral edema, and thrombocytopenia 11 days post-vaccination with Ad26.COV2.S. Medical history included unexplained hematuria and thrombocytopenia starting approximately 3 months prior to vaccination (platelet count of 70,000 at that time), and it was unknown if these conditions were ongoing at event onset. On Day 11, the patient became ill with headache, impaired consciousness, blood clot, suffered a stroke, and was hospitalised. Head CT showed CVST, bleeding into the right hemisphere, and cerebral edema. Heparin-induced platelet antibody (anti-PF4) was positive; D dimer was increased (26,575); thrombocytopenia was present (7,000) and COVID-19 PCR test was negative. After extensive consultation, the event was determined to be a VITT syndrome or TTS. Brain death was confirmed. **MAH Comment:** Although the pre-existing history of thrombocytopenia approximately 3 months prior to vaccine may have contributed, based on evolving knowledge of TTS, per definition from –BC, and considering the low platelet count and temporal relationship to vaccination, the events are assessed to have a plausible relationship with vaccination.
20211009808 US 37 Female	Cerebral venous sinus thrombosis Cerebral haemorrhage	No known allergies or other illnesses Pre-eclampsia (Past)	None	This case (VAERS IDs 1683324, 1770384, and 1766871) concerned a 37-year-old female who experienced CVST, ovarian and renal vein thromboses, thrombocytopenia, and VITT approximately 1 week after vaccination with Ad26.COV2.S. The patient presented to the ED with abdominal pain and headache and was diagnosed with renal and ovarian vein thrombosis, and a large right frontal intraparenchymal cerebral hemorrhage and CVST. Intravenous immunoglobulin and anticoagulation with bivalirudin were started but the patient continued to deteriorate; the patient was taken for urgent craniotomy with external ventricular drain placement due to elevated intracranial pressure. Platelet count was 31,000 (low), fibrinogen 74 (low), D dimer greater than 40 (elevated), and heparin-induced thrombocytopenia test panel optical density 2552 (strongly positive.) The patient was declared brain dead 2 days after the event onset (approximately Day 9) and life support was withdrawn.

Table 126: Summary of Cases Reporting Fatal Cerebrovascular Events in Patients ≤40 Years of Age (n=9)

AER Number Country/Territory Age (Years) Sex	Event(s) of Interest	Medical History/ Concurrent Condition	Concomitant Medications	Summary
				MAH Comment: Based on evolving knowledge of TTS, per definition from BC, the low platelet count and temporal relationship to vaccination, the evens are assessed to have a plausible relationship with vaccination.
20211115184 US 28 Female	Superior sagittal sinus thrombosis Cerebral haemorrhage Subarachnoid haemorrhage	Obesity Hypothyroidism Gastrooesophageal reflux disease Anxiety Depression Drug hypersensitivity Gastric bypass (Past)	Fluticasone Melatonin Ergocalciferol Biotin Diclofenac sodium Escitalopram oxalate Ferrous sulfate Ethinylestradiol; norgestimate Pantoprazole sodium sesquihydrate Linaclotide Cannabis sativa	This case concerned a 28-year-old female who experienced fatal superior sagittal sinus thrombosis, thrombocytopenia, cerebral haemorrhage, and subarachnoid haemorrhage on 13 days post-vaccination with Ad26.COV2.S. Angiogram cerebral was abnormal, and limited clinical details were available. **MAH Comment:** This event is considered potentially associated, with a compatible/suggestive temporal relationship but is not fully assessable due to lack of available information.
20211116416 US 35 Female	Cerebral thrombosis	NR	NR	This case (VAERS ID 1856602) concerned a 35-year-old female who experienced cerebral thrombosis on an unknown date after vaccination with Ad26.COV2.S. This event is considered not assessable due to limited availability of information. **MAH Comment**: The lack of available information (specifically TTO, medical history/concurrent conditions, concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment.
20211238979 Germany 38 Male	Cerebral haemorrhage	Drug abuser Alcohol use COVID-19 (Past)	NR	This case (EVHUMAN, DE-PEI-202100275115) concerned a 38-year-old male who experienced cerebral haemorrhage on an unknown date after vaccination with Ad26.COV2.S. **MAH Comment**: The lack of available information (specifically TTO, concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment.

Table 126: Summary of Cases Reporting Fatal Cerebrovascular Events in Patients ≤40 Years of Age (n=9)

AER Number Country/Territory Age (Years) Sex	Event(s) of Interest	Medical History/ Concurrent Condition	Concomitant Medications	Summary
20220102612 US 4th decade Male	Cerebral haemorrhage	NR	NR	This case concerned a male in his 4th decade who experienced cerebral hemorrhage 1 day post-vaccination with Ad26.COV2.S. This event is considered not assessable due to limited availability of information. **MAH Comment:** The lack of available information (specifically medical history/concurrent conditions, concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment.
20220125923 Netherlands 37 Female	Cerebrovascular accident	NR	NR	This case concerned a 37-year-old female who experienced a fatal cerebrovascular accident on an unknown date after vaccination with Ad26.COV2.S. This event is considered not assessable due to limited availability of information. The event is possible VITT. **MAH Comment:** This event is considered potentially associated, with a compatible/suggestive temporal relationship but is not fully assessable due to lack of available information.

Key: ARSZMP=Agency for Medicinal Products and Medical Devices of the Republic of Slovenia; BC= Brighton Collaboration; CTA=Coronary Angiography; CVST= Cerebral venous sinus thrombosis; ED=Emergency Department; EMEA=MAH=Market Authorisation Holder; MRI=Magnetic Resonance Imaging; n=Number of cases; NR=Not Reported; SARS-CoV2= Severe acute respiratory syndrome coronavirus 2;TTO=Time to Onset; TTS=Thrombosis with Thrombocytopenia Syndrome; US=United States; VAERS= Vaccine Adverse Event Reporting System; VITT= Vaccine-Induced Immune Thrombotic Thrombocytopenia

Non-Fatal Cases in Patients ≤ 40 Years of Age

There a total of were 88 non-fatal cases that occurred in patients ≤ 40 years of age. One the cases was from a clinical trial (VAC31518COV3009) and the remaining were from post-marketing sources. Eleven of the non-fatal cases involved a haemorrhagic event. Of the 87 post-marketing cases, the EOI was outside the 28-day risk window in 25 cases. Of the remaining 62 cases, 14 were confounded by the patients' medical history and/or concurrent diseases. Of the remaining 48 cases, 47 cases lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. In the remaining case, the information that was provided precluded a meaningful medical assessment. Case information for the 88 non-fatal cases that occurred in patients ≤ 40 years of age are included in Appendix 7.27.1.

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

Cumulatively, 21 serious (10 medically confirmed and 11 medically unconfirmed) cases were identified reporting cerebrovascular events in individuals who received the booster dose. Of these cases, 2 were heterologous, and 19 were homologous. CIOMS II LL is presented in Appendix 7.27.2.

O/E Analysis Results

Cerebrovascular Events - Haemorrhagic

Results of the restricted analysis with sensitivity analysis are presented in Table 127.

Table 127: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	**Sex**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	Female	18 to 29	9.24	0.363	(0.168, 0.684)	3.181	(1.472, 5.990)
		30 to 39	13.34	0.384	(0.206, 0.652)	4.982	(2.677, 8.462)
		40 to 49	28.36	0.615	(0.410, 0.886)	9.939	(6.624, 14.332)
		50 to 64	57.74	0.410	(0.311, 0.531)	6.746	(5.119, 8.726)
		65 to 74	34.91	0.312	(0.217, 0.433)	3.444	(2.398, 4.792)
		≥75	30.16	0.208	(0.140, 0.296)	2.585	(1.746, 3.687)
	Male	18 to 29	1.75	0.039	(0.004, 0.151)	0.307	(0.030, 1.199)
		30 to 39	9.79	0.173	(0.082, 0.320)	2.100	(0.998, 3.887)
		40 to 49	20.98	0.290	(0.180, 0.444)	4.694	(2.905, 7.176)
		50 to 64	61.06	0.291	(0.223, 0.374)	4.513	(3.453, 5.796)
		65 to 74	30.20	0.203	(0.137, 0.290)	1.852	(1.251, 2.640)
		≥75	21.37	0.171	(0.107, 0.261)	2.335	(1.452, 3.556)

Table 127: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
EU	Female	18 to 29	5.28	2.189	(0.739, 5.000)	12.430	(4.194, 28.394)
		30 to 39	2.20	0.614	(0.086, 2.105)	2.578	(0.360, 8.836)
		40 to 49	9.20	0.974	(0.450, 1.836)	2.961	(1.368, 5.583)
		50 to 64	11.85	0.364	(0.187, 0.638)	0.971	(0.499, 1.702)
	Male	18 to 29	5.00	1.787	(0.580, 4.170)	9.335	(3.031, 21.785)
		30 to 39	6.00	0.758	(0.278, 1.650)	2.513	(0.922, 5.470)
		40 to 49	3.00	0.189	(0.039, 0.552)	0.521	(0.107, 1.523)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28), and where time-to-onset was day 0 or not reported.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of <1 for both males and females across all age groups. In the EU, the O/E ratio was >1 in the female and male 18 to 29 age groups only. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 in all female and male age groups except the male 18 to 29 age group. In the EU, the sensitivity analysis O/E ratio was >1 in the female: 18 to 29, 30 to 39, 40 to 49 age groups, and male: 18 to 29 and 30 to 39 age groups only.

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

Cerebrovascular Events - Non-Haemorrhagic

Results of the restricted analysis with sensitivity analysis are presented in Table 128.

Table 128: Cerebrovascular Events - Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	Female	18 to 29	9.57	0.269	(0.126, 0.501)	3.545	(1.667, 6.606)
		30 to 39	15.81	0.190	(0.108, 0.310)	3.983	(2.268, 6.487)
		40 to 49	38.87	0.301	(0.214, 0.412)	7.163	(5.090, 9.797)
		50 to 64	68.76	0.153	(0.119, 0.193)	4.404	(3.425, 5.576)
		65 to 74	38.35	0.097	(0.069, 0.133)	1.332	(0.944, 1.826)
		≥75	47.39	0.092	(0.068, 0.122)	1.156	(0.850, 1.535)
	Male	18 to 29	3.62	0.102	(0.025, 0.273)	1.121	(0.279, 3.000)
		30 to 39	13.66	0.128	(0.070, 0.217)	2.108	(1.142, 3.559)
		40 to 49	19.81	0.114	(0.070, 0.177)	2.032	(1.238, 3.145)
		50 to 64	80.71	0.128	(0.102, 0.159)	2.368	(1.880, 2.944)
		65 to 74	35.06	0.073	(0.051, 0.101)	0.818	(0.570, 1.137)
		≥75	24.30	0.064	(0.041, 0.095)	0.909	(0.584, 1.349)

Table 128: Cerebrovascular Events - Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	**Sex**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
EU	Female	18 to 29	6.28	0.715	(0.270, 1.531)	2.486	(0.938, 5.322)
		30 to 39	5.20	0.318	(0.106, 0.731)	0.900	(0.300, 2.068)
	Male	18 to 29	7.31	0.740	(0.305, 1.502)	2.533	(1.043, 5.142)
		30 to 39	10.22	0.625	(0.302, 1.142)	1.778	(0.861, 3.249)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU for all female and male age groups considered. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 in all female age groups and in the male: 18 to 29, 30 to 39, 40 to 49, 50 to 64 age groups. In the EU, the sensitivity analysis O/E ratio was >1 in the females: 18 to 29, and male: 18 to 29, 30 to 39 age groups. Since the previous PBRER O/E DLD (31 August 2021), the O/E ratio increased from <1 to >1 (not statistically significant) for the US male 18 to 29 and EU female 18 to 29 age groups and decreased from >1 to <1 for the US male ≥75 age group.

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

Conclusion

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

16.3.6.5.2. Disseminated Intravascular Coagulation

Introduction

Disseminated intravascular coagulation (DIC) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU,

stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 28), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 9 (6 medically confirmed and 3 medically unconfirmed) cases reporting DIC were identified. All 9 cases were serious and reported a total of 9 serious events.

All 9 cases were reported from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 24 (20 medically confirmed and 4 medically unconfirmed) cases reporting DIC were identified. All 24 cases were serious and reported a total of 24 serious events.

All 24 cumulative cases received were from Post-marketing Sources (including spontaneous and solicited cases). No were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

An overview of these cases is presented in Table 129 below.

Table 129: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Disseminated intravascular coagulation

Case Characteristics		Number of Cases Received During the Reporting Period=9	Number of Cases Received Cumulatively=24
Sex	Male	6	11
	Female	3	13
Age (Years)[a]	18 to 35	1	1
Minimum: 28	36 to 50	3	12
Maximum: 59	51 to 64	3	7
Mean: 45.9	≥65	0	2
Median: 50	NR	2	2
Source	Spontaneous	9	24
Country/Territory[b]	United States	3	13
	Spain	2	2
	Bulgaria	1	1
	Czech Republic	1	1
	France	1	3

Table 129: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Disseminated intravascular coagulation

Case Characteristics		Number of Cases Received During the Reporting Period=9	Number of Cases Received Cumulatively=24
	Germany	1	1
Event Characteristics		**Number of Events=9**	**Number of Events=24**
Seriousness (Event Level)[c]	Serious	9	24
Outcome (Event Level)[c]	Fatal	3	7
	Not resolved	2	6
	Resolving	2	5
	NR	2	6

Key: NR=Not Reported.
a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).
b: Countries/Territories are listed in decreasing order for the current reporting period(25 August 2021 to 24 February 2022).
c: Seriousness and outcome have been presented for the events of interest.

The frequency distribution of the MedDRA PTs of interest reported in cases reporting DIC with the use of Ad26.COV2.S is presented in Table 130 below.

Table 130: Frequency of MedDRA PTs in Cases Reporting Disseminated intravascular coagulation With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Disseminated Intravascular Coagulation	9	0	23	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

Janssen Sponsored Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 9 cases reporting DIC were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 9 cases reported 9 serious EOI. Of these 9 cases, the most frequently reported country/territory of origin was the US (n=3) followed by Spain (n=2). Of the 9 cases, 6 concerned males and 3 females. The age range was 28 to 59 years.

The EOI included disseminated intravascular coagulation (n=9). The reported mean and median TTO was 8.7 days and 7 days, respectively. Where reported (n=7), the outcomes were fatal (n=3), resolving (n=2), and not resolved (n=2). The events with a fatal outcome were DIC (n=3). Case [redacted] was assessed as a fatal case, although the EOI was not noted as the cause of death.

The 1 ICSR literature case received during the reporting period of 25 August 2021 to 24 February 2022 was reviewed, and no information was identified that would change the currently known information on DIC.

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 DIC being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, no cases were identified reporting DIC in an individuals who received the booster dose.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 131.

Table 131: Disseminated Intravascular Coagulation: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	8.30	0.047	(0.021, 0.092)	0.094	(0.041, 0.183)
	≥60	2.67	0.018	(0.003, 0.055)	0.036	(0.006, 0.111)
EU	18 to 59	9.00	0.045	(0.020, 0.085)	0.089	(0.041, 0.170)
	≥60	1.00	0.008	(0.000, 0.045)	0.016	(0.000, 0.089)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28), and where time-to-onset was day 0 or not reported.

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

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

percentage and lower bound background incidence rate) showed an O/E ratio of <1 in the US and EU for both age groups.

A restricted O/E analysis with sensitivity analysis was not required.

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

Conclusion

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

16.3.6.5.3. Thromboembolic and Thrombotic Events Without Thrombocytopenia

Introduction

Thromboembolic and thrombotic events 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.

A cumulative broad and restricted O/E analysis was performed for thrombotic events to include arterial thrombosis, vessel type unspecified and mixed arterial thrombosis, CVST, CVST without thrombocytopenia, DVT, and PE. The O/E results in the US and EU have been stratified by granular age groups (18 to 29, 30 to 39, 40 to 49, 50 to 64, 65 to 74 and ≥75 years) and by sex (female, male) for: Arterial thrombosis, CVST, CVST without thrombocytopenia, and vessel type unspecified and mixed arterial thrombosis only. For DVT and PE, the O/E results in the US and EU have been stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 28) and where TTO was day 0 or not reported. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis was performed for the respective region and age-group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 1,969 (1,013 medically confirmed and 956 medically unconfirmed) cases reporting thromboembolic and thrombotic events were identified. Of these cases, 1,908 cases were serious and 61 nonserious, and reported a total of 2,687 events (2,598 serious; 89 nonserious).

Of these 1,969 cases during the reporting period of 25 August 2021 to 24 February 2022, 152 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 1,809 from Post-marketing Sources (including spontaneous and solicited cases).

Cumulatively, 5,066 (3,054 medically confirmed and 2,012 medically unconfirmed) cases reporting thromboembolic and thrombotic events were identified. Of these cases, 4,935 were serious and 131 nonserious, and reported a total of 7,145 events (6,923 serious; 222 nonserious).

Of these 5,066 cumulative cases received, 277 were reported from Janssen Sponsored Clinical Studies, 48 from Janssen Supported Clinical Study, and 4,741 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 132 below.

Table 132: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Thromboembolic and Thrombotic Events

Case Characteristics		Number of Cases Received During the Reporting Period=1,969	Number of Cases Received Cumulatively=5,066
Sex	Female	831	2,462
	Male	999	2,374
	NR	139	230
Age (Years)[a]	0 to 17	4	5
Minimum: 13	18 to 35	217	586
Maximum: 100	36 to 50	414	1,151
Mean: 53.97	51 to 64	572	1,557
Median: 55	≥65	419	1,183
	Neonate	1	1
	Adult	22	41
	Elderly	6	8
	NR	314	534
Source	Spontaneous	1,797	4,721
	Clinical study (interventional; non-solicited)	159	323
	Clinical study (non-interventional; solicited)	12	20
	Clinical study (non-interventional; non-solicited)	1	2
Country/Territory[b]	United States	1,229	3,731
	Germany	215	330
	France	69	128
	Netherlands	51	120
	Italy	47	109
	South Africa	38	91
	Brazil	34	64

Table 132: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Thromboembolic and Thrombotic Events

Case Characteristics		Number of Cases Received During the Reporting Period=1,969	Number of Cases Received Cumulatively=5,066
	Philippines	31	40
	Spain	26	74
	Greece	23	35
	Austria	22	29
	Belgium	20	43
Event Characteristics		**Number of Events=2,687**	**Number of Events=7,145**
Seriousness (Event Level)[c]	Serious	2,598	6,923
	Nonserious	89	222
Outcome (Event Level)[c]	Not resolved	899	2,801
	Resolved	368	1,054
	Resolving	293	633
	Fatal	281	583
	Resolved with sequelae	64	110
	NR	782	1,964

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥20 were presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting thromboembolic and thrombotic events with the use of Ad26.COV2.S is presented in Table 133 below. A single case may contain more than 1 EOI.

Table 133: Frequency of MedDRA PTs in Cases Reporting Thromboembolic and Thrombotic Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis	480	2	1,313	3
Pulmonary embolism	331	2	930	5
Cerebrovascular accident	274	0	644	1
Deep vein thrombosis	230	13	753	22
Myocardial infarction	161	0	299	0
Acute myocardial infarction	80	0	164	0
Pulmonary thrombosis	73	0	177	0
Ultrasound Doppler abnormal	60	12	198	43
Transient ischaemic	47	6	138	7

Table 133: Frequency of MedDRA PTs in Cases Reporting Thromboembolic and Thrombotic Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
attack				
Hemiparesis	49	0	163	0
Cerebral infarction	44	0	91	0
Ischaemic stroke	44	0	111	0
Cerebral venous sinus thrombosis	41	0	127	0
Thrombosis with thrombocytopenia syndrome	34	2	42	2
Hemiplegia	30	0	69	0
Cerebral thrombosis	28	0	80	0
Superficial vein thrombosis	15	9	39	48
Thrombophlebitis	13	11	25	28
Intracardiac thrombus	23	0	42	0
Portal vein thrombosis	20	0	43	0

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

a: The MedDRA PTs of interest with frequency ≥20 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 EOI.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 152 cases reporting thromboembolic and thrombotic events were retrieved from Janssen Sponsored Clinical Studies. Of the 152 cases, 95 were reported from VAC31518COV3001, 53 from VAC31518COV3009, 2 from VAC31518COV2008, and 1 each from VAC31518COV2009 and VAC31518COV3005. These 152 cases reported 122 serious EOI. Of these 152 cases, the most frequently reported country/territory of origin was the US (n=74). Of these 152 cases, 96 concerned males and 56 females. The age range was 30 to 87 years.

The EOI (n≥13) included cerebrovascular accident (n=27), acute myocardial infarction (n=26), myocardial infarction (n=20), pulmonary embolism (n=19), deep vein thrombosis (n=17), and transient ischaemic attack (n=13). The mean and median TTO was 238 days and 246 days, respectively. Where reported (n=152), the outcomes were resolved (n=75), resolving (n=37), not resolved (n=16), fatal (n=13), and resolved with sequelae (n=11). The Sponsor and Investigator's causality assessment of the EOI was reported as not related (n=149), as related (n=4), and the Sponsor assessed as not related with the Investigator causality assessed as related (n=2).

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 8 cases reporting thromboembolic and thrombotic events were retrieved from Janssen Supported Clinical Studies. Of the 8 cases, 4 were reported from VAC31518COV3021, 3 from VAC31518COV3012, and

1 from VAC31518COV4007. These 8 cases reported 8 serious EOI. Of these 8 cases, the most frequently reported country/territory of origin was South Africa (n=7). Of these 8 cases, 6 concerned females and 2 males. The age range was 29 to 80 years.

The EOI included pulmonary embolism (n=5) and deep vein thrombosis, myocardial infarction, portal vein thrombosis, and superficial vein thrombosis (n=1 each). The mean and median TTO was 121.5 days and 39 days, respectively. Where reported (n=8), the outcomes were resolving (n=5), resolved (n=2), and not resolved (n=1). The Company and Sponsor's causality assessment of the EOI was reported as not related (n=6), Company assessed as not related with the Sponsor causality assessed as related (n=1), Company assessed as not related with the Sponsor causality assessed as not reported (n=1), and Company assessed as related with the Sponsor causality assessed as not related (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 1,809 cases reporting thromboembolic and thrombotic events were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 1,809 cases reported 2,468 serious EOI. Of these 1,809 cases, the most frequently reported country/territory of origin was the US (n=1,155) followed by Germany (n=215), and France (n=68). Of the 1,809 cases, 901 concerned males, 769 females, and 139 had no sex reported. The age range was 13 to 100 years.

The EOI (n≥140) included thrombosis (n=479), pulmonary embolism (n=309), cerebrovascular accident (n=247), deep vein thrombosis (n=225), and myocardial infarction (n=140). The reported mean and median TTO was 57.4 days and 24 days, respectively. Where reported (n=1,745), the outcomes were not resolved (n=882), resolved (n=291), fatal (n=268), resolving (n=251), and resolved with sequelae (n=53). The events (n≥10) with a fatal outcome were thrombosis (n=53), pulmonary embolism (n=38), myocardial infarction (n=35), cerebrovascular accident (n=23), and cerebral venous sinus thrombosis (n=10).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information of thromboembolic and thrombotic events.

Fatal Cases

Overall, 268 fatal events were reported in 193 cases. Of these cases, 88 concerned males, 80 females, and 25 did not report sex. The age range was 19 to 97 years. Among patients where age was reported (134/193), 17 were in the age range of 18 to 35 years, 28 were in the age range of 36 to 50 years, 34 were in the age range of 51 to 64 years, and 55 were ≥ 65 years. The mean and median TTO reported in these 268 fatal events were 79.7 days and 33 days, respectively

The frequency distribution of the 268 fatal MedDRA PTs of interest reported in these 193 cases is presented in Table 134 below. A single case may contain more than 1 EOI.

Table 134: Frequency Distribution of Fatal MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Thromboembolic and Thrombotic Events (Fatal Events=268)

MedDRA PTs	Fatal Outcome[a]
Thrombosis	53
Pulmonary embolism	38
Myocardial infarction	35
Cerebrovascular accident	23
Cerebral venous sinus thrombosis	10

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with frequency ≥10 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 EOI.

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 thromboembolic and thrombotic events being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 86 (42 medically confirmed and 44 medically unconfirmed) cases were identified reporting thromboembolic and thrombotic events in individuals who received the booster dose. There were 85 serious cases and 1 nonserious case. Of these cases, 16 were heterologous and 70 were homologous. CIOMS II LL is presented in Appendix 7.28.

O/E Analysis Results

Arterial Thrombosis (with or without Thrombocytopenia)

Results of the restricted analysis with sensitivity analysis are presented in Table 135.

Table 135: Arterial Thrombosis: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	Female	18 to 29	3.11	0.255	(0.055, 0.731)	0.797	(0.171, 2.290)
		30 to 39	12.16	0.463	(0.240, 0.805)	1.167	(0.606, 2.032)
	Male	18 to 29	8.26	0.139	(0.061, 0.271)	0.323	(0.142, 0.630)
EU	Female	18 to 29	3.00	0.236	(0.049, 0.691)	0.740	(0.153, 2.163)
	Male	18 to 29	3.31	0.170	(0.039, 0.473)	0.487	(0.111, 1.358)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28) only.
b: Poisson exact confidence interval (95% CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU for all age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 in the female: 30 to 39 age group. In the EU, the sensitivity analysis O/E ratio was <1 for all the age groups considered. Since the previous PBRER O/E DLD (31 August 2021), the O/E ratio increased from <1 to >1 (not statistically significant) for the US female 30 to 39 age group only.

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

Mixed (Venous or Arterial) Thrombosis with or without Thrombocytopenia

Results of the restricted analysis with sensitivity analysis are presented in Table 136.

Table 136: Vessel Type Unspecified and Mixed Arterial and Venous Thrombosis: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	**Sex**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	Female	18–29	45.61	0.728	(0.532, 0.972)	1.753	(1.282, 2.342)
		30–39	81.29	0.690	(0.548, 0.858)	1.535	(1.220, 1.908)
		40–49	143.46	0.667	(0.562, 0.785)	1.433	(1.208, 1.687)
	Male	18–29	14.33	0.270	(0.149, 0.451)	0.664	(0.366, 1.108)
		30–39	53.40	0.414	(0.310, 0.540)	0.916	(0.687, 1.197)
EU	Female	18–29	14.62	0.261	(0.145, 0.433)	0.641	(0.356, 1.064)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28) only.
b: Poisson exact confidence interval (95% CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in the US and EU for all age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in all the US female age groups considered. In the EU, the sensitivity analysis O/E ratio was <1 in the female 18 to 29 age group. Since the previous PBRER O/E DLD (31 August 2021), the O/E ratio increased from <1 to >1 (statistically significant) for the US female: 18 to 29, 30 to 39 and 40 to 49 age groups.

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

Cerebral Venous Sinus Thrombosis with or without Thrombocytopenia

Results of the restricted analysis with sensitivity analysis are presented in Table 137.

Table 137: Cerebral Venous Sinus Thrombosis (CVST): Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	Female	18 to 29	7.11	10.361	(4.202, 21.234)	162.323	(65.831, 332.664)
		30 to 39	13.16	20.187	(10.797, 34.411)	311.461	(166.579, 530.916)
		40 to 49	16.17	14.650	(8.402, 23.731)	105.928	(60.751, 171.591)
		50 to 64	9.34	5.010	(2.330, 9.403)	37.673	(17.524, 70.708)
		65 to 74	2.14	1.797	(0.241, 6.253)	11.787	(1.582, 41.011)
		≥75	1.08	1.150	(0.037, 6.078)	6.962	(0.223, 36.807)
	Male	18 to 29	2.00	1.169	(0.142, 4.224)	10.163	(1.231, 36.714)
		30 to 39	1.00	0.750	(0.019, 4.181)	5.589	(0.142, 31.141)
		40 to 49	7.00	13.203	(5.308, 27.203)	237.653	(95.549, 489.657)
		50 to 64	5.00	1.675	(0.544, 3.909)	9.109	(2.958, 21.258)
		65 to 74	1.00	0.975	(0.025, 5.431)	7.365	(0.186, 41.035)
		≥75	1.00	1.129	(0.029, 6.291)	7.754	(0.196, 43.200)
EU	Female	18 to 29	5.58	7.826	(2.741, 17.502)	122.605	(42.940, 274.190)
		30 to 39	4.00	5.295	(1.443, 13.557)	81.691	(22.258, 209.163)
		40 to 49	8.00	6.054	(2.613, 11.928)	43.772	(18.897, 86.248)
		50 to 64	8.00	4.108	(1.774, 8.095)	30.893	(13.337, 60.871)
		≥75	1.00	1.119	(0.028, 6.237)	6.778	(0.172, 37.766)
	Male	18 to 29	7.42	4.107	(1.705, 8.296)	35.699	(14.818, 72.110)
		30 to 39	4.00	2.606	(0.710, 6.673)	19.412	(5.289, 49.703)
		40 to 49	3.00	4.714	(0.972, 13.777)	84.856	(17.499, 247.985)
		50 to 64	3.00	0.972	(0.200, 2.840)	5.285	(1.090, 15.444)
		65 to 74	0.00	0.000	(0.000, 4.205)	0.000	(0.000, 31.773)
		≥75	1.00	1.332	(0.034, 7.424)	9.151	(0.232, 50.985)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of >1 across all age groups for both males and females except for the male 30 to 39 and 65 to 74 age group. In the EU, an O/E ratio of >1 was shown for both males and females across all age groups except for the male 50 to 64 and 65 to 74 age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in both the US and EU across all age groups for both males and females except for the EU male 65 to 74 age group.

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

Cerebral Venous Sinus Thrombosis Without Thrombocytopenia

Results of the restricted analysis with sensitivity analysis are presented in Table 138.

Table 138: CVST (Without Thrombocytopenia): Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February2022)

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	3.00	4.372	(0.902, 12.776)	68.491	(14.124, 200.159)
		30 to 39	6.00	9.204	(3.378, 20.033)	142.004	(52.113, 309.082)
		40 to 49	7.00	6.342	(2.550, 13.067)	45.856	(18.437, 94.481)
		50 to 64	5.00	2.966	(0.963, 6.921)	25.209	(8.185, 58.830)
		65 to 74	2.00	1.926	(0.233, 6.956)	14.354	(1.738, 51.851)
		≥75	1.00	1.241	(0.031, 6.914)	8.595	(0.218, 47.888)
	Male	18 to 29	0.00	0.000	(0.000, 2.215)	0.000	(0.000, 20.308)
		30 to 39	1.00	0.750	(0.019, 4.181)	5.589	(0.142, 31.141)
		40 to 49	4.00	7.545	(2.056, 19.317)	135.802	(37.001, 347.707)
		50 to 64	4.00	1.340	(0.365, 3.431)	7.288	(1.986, 18.659)
		65 to 74	1.00	1.133	(0.029, 6.313)	10.198	(0.258, 56.818)
		≥75	1.00	1.463	(0.037, 8.149)	12.376	(0.313, 68.954)
EU	Female	18 to 29	2.58	3.618	(0.626, 11.401)	56.688	(9.806, 178.621)
		30 to 39	1.00	1.324	(0.034, 7.375)	20.423	(0.517, 113.789)
		40 to 49	4.00	3.027	(0.825, 7.750)	21.886	(5.963, 56.036)
		50 to 64	4.00	2.272	(0.619, 5.816)	19.308	(5.261, 49.436)
		≥75	1.00	1.305	(0.033, 7.270)	9.038	(0.229, 50.355)
	Male	18 to 29	3.42	1.945	(0.459, 5.341)	17.825	(4.208, 48.959)
		30 to 39	2.00	1.303	(0.158, 4.707)	9.706	(1.175, 35.062)
		40 to 49	0.00	0.000	(0.000, 5.797)	0.000	(0.000, 104.341)
		50 to 64	2.00	0.648	(0.078, 2.340)	3.523	(0.427, 12.727)
		65 to 74	0.00	0.000	(0.000, 4.888)	0.000	(0.000, 43.994)
		≥75	1.00	1.726	(0.044, 9.618)	14.606	(0.370, 81.380)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of >1 for all female and male age groups except the male 18 to 29 and 30 to 39 age groups. In the EU, the O/E ratio was >1 for all female age groups and the male: 18 to 29, 30 to 39 and ≥75 age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 for all female and male age groups except the male 18 to 29 age group. In the EU, the sensitivity analysis O/E ratio was >1 for both males and females in all age groups considered except the male 40 to 49 and 65 to 74 age groups. Since the previous PBRER O/E DLD (31 August 2021), the O/E ratio increased from <1 to >1 (statistically significant) for the EU female: 30 to 39 age group and increased from <1 to >1 (not statistically significant) in the EU male: 30 to 39 and 50 to 64 age groups.

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

The O/E analysis for data reported for deep vein thrombosis and pulmonary embolism in the US and EU:

Deep Vein Thrombosis with or without Thrombocytopenia

Given ACCESS Rates were not available separately for DVT with or without thrombocytopenia, the O/E analyses were conducted using background incidence rates selected by the MAH (Huang 2014). A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSR that occurred within the risk window (day: 1 to 28), and where TTO was day 0 or not reported. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include: exposure calculations, risk windows, background incidence rates, and search strategy). Results of the broad analysis are presented in Table 139.

Table 139: Deep Vein Thrombosis: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Broad O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	397.22	0.660	(0.597, 0.728)	5.470	(4.945, 6.036)
	≥60	181.45	0.360	(0.309, 0.416)	1.277	(1.098, 1.477)
EU	18 to 59	163.11	0.238	(0.202, 0.277)	1.968	(1.678, 2.294)
	≥60	76.82	0.182	(0.144, 0.228)	0.647	(0.510, 0.809)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 for both the US and EU for both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US for both age groups. In the EU, the sensitivity analysis O/E ratio was >1 for the 18 to 59 age group only.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was > 1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the window (day: 1 to 28) only. Results of this analysis are presented in Table 140.

Table 140: Deep Vein Thrombosis: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	323.90	0.538	(0.481, 0.600)	4.461	(3.988, 4.974)
	≥60	145.02	0.287	(0.243, 0.338)	1.021	(0.861, 1.201)
EU	18 to 59	131.60	0.192	(0.160, 0.227)	1.588	(1.328, 1.883)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28) only.
b: Poisson exact confidence interval (95% CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 for the US and EU for all age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US and EU for all age groups concerned.

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

Pulmonary embolism

Given ACCESS Rates were not available separately for PE with or without thrombocytopenia, the O/E analyses were conducted using background incidence rates selected by the MAH (Huang 2014). A broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59, ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 28), and where TTO was day 0 or not reported. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include: exposure calculations, risk windows, background incidence rates, and search strategy). Results of the broad analysis are presented in Table 141.

Table 141: Pulmonary Embolism: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	332.23	0.634	(0.568, 0.706)	9.150	(8.193, 10.189)
	≥60	216.20	0.284	(0.247, 0.324)	0.733	(0.638, 0.837)
EU	18 to 59	115.36	0.193	(0.159, 0.232)	2.784	(2.299, 3.340)
	≥60	72.60	0.114	(0.089, 0.144)	0.294	(0.231, 0.370)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 28), and where time-to-onset was day 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 for both the US and EU for both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US and EU for the 18 to 59 age group only.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was > 1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the window (day: 1 to 28) only. Results of this analysis are presented in Table 142.

Table 142: Pulmonary Embolism: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

	Restricted O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	251.86	0.481	(0.423, 0.544)	6.937	(6.107, 7.849)
EU	18 to 59	87.92	0.147	(0.118, 0.181)	2.122	(1.701, 2.614)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1-28) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 in both the US and EU 18 to 59 age group. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US and EU 18 to 59 age group.

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

Conclusion

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

The phenotypes of thrombotic/thromboembolic events of relevance following Ad26.COV2.S are already described in more detail in other sections of this report (including VTE, Cerebrovascular Events, Coronary Artery Disease, and TTS). The Company proposes following the remaining phenotypes of thrombotic events through routine pharmacovigilance activities.

16.3.6.6. Hepatic Disorders

16.3.6.6.1. Acute Hepatic Failure

Introduction

Acute hepatic failure is listed as an AESI in the cRMP, EU RMP, and 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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 14) and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 47 (20 medically confirmed and 27 medically unconfirmed) cases reporting acute hepatic failure were identified. Of these cases, 41 were serious and 6 nonserious, and reported a total of 52 events (43 serious; 9 nonserious).

Of these 47 cases during the reporting period of 25 August 2021 to 24 February 2022, 7 were reported from Janssen Sponsored Clinical Studies and 40 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 79 (38 medically confirmed and 41 medically unconfirmed) cases reporting acute hepatic failure were identified. Of these cases, 71 were serious and 8 nonserious, and reported a total of 88 events (72 serious; 16 nonserious).

Of these 79 cumulative cases received, 7 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 70 from Post-marketing Sources (including spontaneous and solicited cases.

An overview of these cases is presented in Table 143 below.

Table 143: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Acute Hepatic Failure

Case Characteristics		Number of Cases Received During the Reporting Period=47	Number of Cases Received Cumulatively=79
Sex	Male	24	37
	Female	22	38
	NR	1	4
Age (Years)[a]	18 to 35	5	11
Minimum:24	36 to 50	7	12
Maximum:85	51 to 64	17	26
Mean:56.1	≥65	12	18
Median:58	Adult	1	1
	Elderly	0	1
	NR	5	10
Sources	Spontaneous	40	70
	Clinical study (interventional; non-solicited)	7	9
Country/Territory[b]	United States	27	53
	Brazil	4	4
	France	3	4
	Netherlands	3	3
	Germany	2	2
	Austria	1	1
	China, PRC	1	1
	Colombia	1	1
	Croatia	1	1
	Hungary	1	1
	Philippines	1	1
	South Africa	1	3
	Spain	1	2
Event Characteristics		**Number of Events=52**	**Number of Events=88**
Seriousness (Event Level)[c]	Serious	43	72
	Nonserious	9	16
Outcome (Event Level)[c]	Not resolved	14	22
	Fatal	10	15
	Resolved	6	14
	Resolving	5	7
	NR	17	30

Key: NR=Not Reported; PRC=People's Republic of China.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in descending order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting acute hepatic failure with the use of Ad26.COV2.S is presented in Table 144 below. A single case may contain more than 1 EOI.

Table 144: Frequency of MedDRA PTs in Cases Reporting Acute Hepatic Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Hepatic steatosis	7	3	11	6
Hepatic cirrhosis	8	0	8	0
Liver disorder	1	6	2	9
Ascites	5	0	7	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest with frequency ≥5 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 7 cases reporting acute hepatic failure were retrieved from Janssen Sponsored Clinical Studies. Five cases were from VAC31518COV3001, and 2 from VAC31518COV3009. These 7 serious cases reported 7 serious EOI. Of these 7 cases, the most frequently reported country/territory of origin was the US (n=5) followed by Brazil and South Africa (n=1 each). Of these 7 cases, 1 concerned a female and 6 males. The age range was 50 to 85 years.

The EOI included drug-induced liver injury and hepatic failure (n=2), hepatic encephalopathy, liver injury, and varices oesophageal (n=1 each). The mean and median TTO was 231.8 days and 239 days, respectively. Where reported (n=7), the outcomes were resolved, resolving, and fatal (n=2 each), and not resolved (n=1). In 5 cases, the EOI were outside the risk window of 14-days, while the remaining 2 cases were confounded by concurrent chemotherapy with capecitabine in 1 case, and underlying human immunodeficiency virus (HIV) treated with atazanavir, efavirenz, lamivudine, and tenofovir in the other. The Sponsor and Investigator's causality assessment of the EOI was reported as not related for all cases (n=7).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 40 cases reporting acute hepatic failure were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 40 cases reported 36 serious EOI. Of these 40 cases, the most frequently reported country/territory of origin was the US (n=22) followed by Brazil, France,, and the

Netherlands (n=3 each). Of the 40 cases, 21 concerned females, 18 males, and 1 had no sex reported. The age range was 24 to 80 years.

The EOI (n≥5) included hepatic steatosis (n=10), hepatic cirrhosis (n=8), liver disorder (n=7), and ascites (n=5). The reported mean and median TTO was 72.6 days and 30 days, respectively. Where reported (n=28), the outcomes were not resolved (n=13), fatal (n=8), resolved (n=4), and resolving (n=3). The EOI with a fatal outcome were hepatic cirrhosis (n=3), hepatic steatosis, acute hepatic failure (n=2), and nonalcoholic fatty liver disease (n=1).

ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed. There was 1 case identified from a literature source which concerned a 57-year-old male, without significant medical history, nor on any long-term treatment, who 10 days post-vaccination with Ad26.COV2.S experienced thrombocytopenia, DIC, and thrombosis on multiple sites, including partial portal vein thrombosis and right and middle hepatic vein thrombosis with hepatic cytolysis. Vaccine-Induced prothrombotic immune thrombocytopenia syndrome was suspected. Differential diagnostics ruled out other aetiologies, such as infection, immune thrombocytopenic purpura, drugs, hypersplenism, genetic disorder, cancer, trauma, surgery, immobilisation, thrombotic thrombocytopenic purpura, and thrombophilia. Anti-PF4 antibodies returned positive at 1.181 IU/L (n greater than 0.5), platelet aggregation test returned normal. The patient received corticosteroids 0.75 mg/kg and intravenous immunoglobulins at 2 g/kg over 2 days, and biological parameters improved over the next few days. The event of liver failure was secondary to the thrombotic event compromising the portal vein and was not directly associated to the vaccine.

Fatal Cases

During the reporting period, the Company received a total of 8 cases of acute hepatic failure with a fatal outcome. These cases concerned 3 females and 5 males with an age range from 24 to 72 years. When reported, the TTO in these cases ranged from 1 to 157 days. The most frequently reported PTs associated with a fatal outcome were hepatic cirrhosis (n=3), acute hepatic failure (n=2) and hepatic steatosis (n=2). From the 8 fatal cases, in 3 the EOI was outside the 14-day risk window, in 2 there was missing information on completed clinical course with laboratory workup and imaging for barring any meaningful medical assessment, and 2 were confounded by underlying hepatitis B infection and alcoholism.

The last case concerned a 24-year-old female without any chronic health conditions, who experienced acute hepatic failure of unknown aetiology, without hepatic coma 6 days post-vaccination with Ad26.COV2.S. The patient had a gastrointestinal haemorrhage, multiple organ dysfunction syndrome, brain oedema, and cerebellar tonsillar herniation. The patient was listed for orthotopic liver transplantation but was determined not to be a candidate due to worsening neurological status and passed away 9 days post-vaccination. The cause of death was reported as cerebellar tonsillar herniation, acute liver failure, and multi-organ failure. Despite a close temporal association, no clinical details were provided regarding the event of fulminant

hepatic failure (including laboratory, biopsy or autopsy results). In the absence of a clear diagnosis, the event is not assessable for causality as per WHO AEFI causality framework.

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 acute hepatic failure being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 1 nonserious (medically unconfirmed) case was identified reporting acute hepatic failure in an individual who received the booster dose. This case was homologous. CIOMS II LL is presented in Appendix 7.29.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 145.

Table 145: Acute Hepatic Failure: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	25.21	8.801	(5.707, 12.971)	17.602	(11.414, 25.942)
	≥60	10.70	10.653	(5.257, 19.210)	21.305	(10.515, 38.421)
EU	18 to 59	3.00	0.030	(0.006, 0.089)	0.074	(0.015, 0.217)
	≥60	7.00	0.129	(0.052, 0.265)	0.301	(0.121, 0.620)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 14) and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed for the US an O/E ratio of >1 for both age groups. In the EU, the O/E ratio was <1 for both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) again showed an O/E ratio of >1 in the US for both age groups. In the EU, the O/E ratio was again <1 for both age groups.

A restricted O/E analysis with sensitivity analysis was performed for those age groups where the O/E ratio was >1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the window (day: 1 to 14) only.

Results of the restricted O/E and sensitivity analysis for acute hepatic failure are presented in Table 146.

Table 146: Acute Hepatic Failure: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Restricted O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	11.00	3.840	(1.917, 6.871)	7.680	(3.834, 13.742)
	≥60	4.00	3.982	(1.085, 10.196)	7.965	(2.170, 20.392)

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

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

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

A review of the acute hepatic failure O/E results for the US and EU restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) and sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US for both age groups.

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

Conclusion

Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new safety information was identified during the reporting period for acute hepatic failure. The Company will continue to closely monitor this event as an AESI.

16.3.6.7. Renal Disorders

16.3.6.7.1. Acute Kidney Failure

Introduction

Acute kidney failure is listed as an AESI in the cRMP, EU RMP, and US PVP.

During the reporting period, the Company performed an aggregate evaluation of cases of nephrotic syndrome and minimal change disease (MCD) following a request by the EMA PRAC Rapporteur on the final Assessment Report for the fifth Monthly Summary Safety Report (MSSR). The outcome of this evaluation was presented in the 6th MSSR with an additional analysis performed in the seventh MSSR.

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.

A cumulative broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18-59 and ≥60. Observed counts included EOI originating from valid initial and booster ICSRs that occurred within the risk window (day: 1 to 14), and where TTO was day 0 or not reported. EOI from both valid and invalid case were included. If the O/E ratio was >1 in the broad sensitivity analysis, a cumulative restricted analysis with sensitivity analysis was performed for the respective region and age group (see Appendix 6.1 for full methodology to include exposure calculations (for initial and booster doses), risk windows, background incidence rates, and search strategy).

Results/Discussion

During the reporting period of 25 August 2021 to 24 February 2022, 91 (65 medically confirmed and 26 medically unconfirmed) cases reporting acute kidney failure were identified. All 91 cases were serious and reported a total of 111 events (109 serious, 2 nonserious).

Of these 91 cases during the reporting period of 25 August 2021 to 24 February 2022, 9 were reported from Janssen Sponsored Clinical Studies and 82 from Post-marketing Sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 152 (116 medically confirmed and 36 medically unconfirmed) cases reporting acute kidney failure were identified. All 152 cases were serious and reported a total of 182 events (180 serious, 2 nonserious).

Of these 152 cumulative cases received, 17 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 133 from Post-marketing Sources (including spontaneous and solicited cases.

An overview of these cases is presented in Table 147 below.

Table 147: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

Case Characteristics		Number of Cases Received During the Reporting Period=91	Number of Cases Received Cumulatively=152
Sex	Male	53	84
	Female	35	63
	NR	3	5
Age (Years)[a]	18 to 35	3	8
Minimum:18	36 to 50	12	20
Maximum:95	51 to 64	32	55
Mean:62.9	≥65	37	59
Median:64	Adult	1	1
	Elderly	1	1
	NR	5	8
Source	Spontaneous	81	132
	Clinical study	9	19

Table 147: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

Case Characteristics		Number of Cases Received During the Reporting Period=91	Number of Cases Received Cumulatively=152
	(interventional; non-solicited)		
	Clinical study (non-interventional; solicited)	1	1
Country/Territory[b]	United States	65	112
	South Africa	4	6
	Germany	3	3
	Hungary	3	3
	Greece	2	4
	Philippines	2	2
	Austria	1	2
	Croatia	1	1
	Czech Republic	1	1
	France	1	1
	Italy	1	2
	Lesotho	1	1
	Netherlands	1	1
	Poland	1	1
	Slovenia	1	1
	Spain	1	2
	Tanzania, United Republic of	1	1
	United Kingdom	1	1
Event Characteristics		**Number of Events=111**	**Number of Events=182**
Seriousness (Event Level)[c]	Serious	109	180
	Nonserious	2	2
Outcome (Event Level)[c]	Fatal	34	49
	Not resolved	28	53
	Resolved	20	34
	Resolving	8	11
	Resolved with sequelae	1	1
	NR	20	34

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories are listed in descending order for the current reporting period (25 August 2021 to 24 February 2022).

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

The frequency distribution of the MedDRA PTs of interest reported in cases reporting acute kidney failure with the use of Ad26.COV2.S is presented in Table 148 below. A single case may contain more than 1 EOI.

Table 148: Frequency of MedDRA PTs in Cases Reporting Acute Kidney Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute kidney injury	56	1	91	1
Renal failure	20	0	32	0
Renal impairment	14	0	22	0
Haemofiltration	5	0	5	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest with frequency ≥5 were sorted by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may report more than 1 event of interest.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 9 cases reporting acute kidney failure were retrieved from Janssen Sponsored Clinical Studies. Six cases were from VAC31518COV3001 and 3 from VAC31518COV3009. These 9 cases reported 8 serious EOI. Of these 9 cases, the reported country/territory of origin were the US (n=5), followed by South Africa (n=2), Spain and the UK (n=1 each). Of these 9 cases, 5 concerned females and 4 males. The age range was 40 to 88 years.

The EOI included acute kidney injury (n=6), renal failure (n=2), and renal impairment (n=1). The mean and median TTO was 267 days and 242 days, respectively. Where reported (n=9), the outcomes were resolved (n=6), not resolved (n=2), and fatal (n=1). In all 9 cases the EOI was outside the 14-day risk window. The Sponsor and Investigator's causality assessment for all EOI was reported as not related (n=9).

Janssen Supported Clinical Studies

There were no cases retrieved from the search of the Company global safety database during the reporting period of 25 August 2021 to 24 February 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 82 cases reporting acute kidney failure were retrieved from Post-marketing sources (including spontaneous and solicited cases). These 82 cases reported 101 serious EOI. Of these 82 cases, the most frequently reported country/territory of origin was the US (n=60) followed by Germany and Hungary (n=3 each). Of the 82 cases, 49 concerned males, 30 females, and 3 had no sex reported. The age range was 18 to 95 years.

The EOI included acute kidney injury (n=51), renal failure (n=18), and renal impairment (n=13). The reported mean and median TTO was 108 days and 84 days, respectively. Where reported (n=82), the outcomes were fatal (n=33), not resolved (n=26), resolved (n=14), resolving (n=8), and resolved with sequelae (n=1). The most frequently reported EOI with fatal outcome were acute kidney injury (n=15), followed by renal failure (n=7).

Additionally, 6 ICSR literature cases received during the reporting period of 25 August 2021 to 24 February 2022 were reviewed, and no information was identified that would change the currently known information on acute kidney injury.

Fatal Cases

During the reporting period, a total of 28 cases of acute kidney failure with a fatal outcome were received. These cases concerned 8 females and 20 males with an age range from 20 to 95 years. When reported, the TTO in these cases ranged from 1 to 256 days. The most frequently reported PTs associated with a fatal outcome were acute kidney injury (n=15), renal failure (n=7) and renal impairment (n=4).

From these 28 fatal cases, 17 had a TTO for the EOI outside the 14-day risk window. Of the 11 cases occurring within the 14-day risk window, 4 were confounded by the patients' medical history (such as chronic kidney disease, renal cancer) and/or concurrent diseases (such as rhabdomyolysis, sepsis, diabetic ketoacidosis). The remaining 7 cases were lacking information, including missing TTO, medical history, concomitant medication and complete aetiologic and diagnostic workup, barring any meaningful medical assessment.

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 acute kidney failure being causally associated with Ad26.COV2.S.

Booster Dose

Cumulatively, 2 serious (1 medically confirmed and 1 medically unconfirmed) cases were identified reporting acute kidney failure in individuals who received the booster dose. Of these cases, 1 was heterologous and 1 homologous. CIOMS II LL is presented in Appendix 7.30.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 149.

Table 149: Acute Kidney Failure: Broad O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	22.90	0.210	(0.133, 0.316)	0.451	(0.286, 0.677)
	≥60	30.02	0.786	(0.531, 1.123)	1.686	(1.138, 2.406)
EU	18 to 59	12.84	0.065	(0.034, 0.111)	0.148	(0.078, 0.253)
	≥60	4.15	0.006	(0.002, 0.015)	0.012	(0.003, 0.031)

Key: CI=Confidence Interval; EOI=Event 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/invalid cases) that occurred within the risk window (day: 1 to 14), and where time-to-onset was day 0 or not reported.

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

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 for the US and EU in both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed for the US an O/E ratio of >1 in the ≥60 age group. In the EU, the O/E ratio was <1 for both age groups.

A restricted O/E analysis with sensitivity analysis was performed where the O/E ratio was > 1 in the broad sensitivity analysis. This included EOI that were known to have occurred within the risk window (day: 1 to 14) only. Results of the broad O/E and sensitivity analysis for acute kidney failure are presented in Table 150.

Table 150: Acute Kidney Failure: Restricted O/E and Sensitivity Analysis Results (Cumulative to 24 February 2022)

O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	≥60	18.00	0.472	(0.279, 0.745)	1.011	(0.599, 1.598)

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

a: Counts included EOI (from valid/invalid cases) that occurred within the risk window (day: 1 to 14) only.

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

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate background incidence rate) showed an O/E ratio of <1 for the US ≥60 age group. A sensitivity analysis (applying a 50% reporting percentage and lower bound background incidence rate) showed an O/E ratio of >1 in the US ≥60 age group. Since the previous PBRER O/E DLD (31 August 2021), the O/E ratio increased from <1 to >1 (not statistically significant) for the US ≥60 age group.

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

Conclusion

The cumulative review of cumulative cases of nephrotic syndrome and MCD was triggered following a literature case report in close temporal association that suggested a possible association between COVID-19 Janssen vaccine and MCD. The Company concluded that despite a couple of cases of MCD in close temporal association with the vaccine where individual causality cannot be excluded, overall there is insufficient information to conclude a causal link between Ad26.COV2.S and MCD.

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 both during the interval and cumulative, and an O/E analysis, no new safety information was identified during the reporting period for acute kidney failure. The Company will continue to closely monitor acute kidney failure as an AESI.

16.3.7. Death

Introduction

An overview of fatal cases reported with the use of Ad26.COV2.S vaccine is provided in this report.

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 the reporting period of 25 August 2021 to 24 February 2022, 1,269 (783 medically confirmed and 486 medically unconfirmed) cases reporting a fatal outcome were identified.

Of these 1,269 cases during the reporting period of 25 August 2021 to 24 February 2022, 102 were reported from Janssen Sponsored Clinical Studies, 178 from Janssen Supported Clinical Studies, and 989 from Post-marketing Sources (including spontaneous and solicited cases). These 1,269 cases reported a total of 2,989 events with a fatal outcome.

Cumulatively, 1,982 (1247 medically confirmed and 735 medically unconfirmed) cases reporting a fatal outcome were identified. These 1,982 cases reported a total of 4,979 events with a fatal outcome.

Of these 1,982 cumulative cases received, 185 were reported from Janssen Sponsored Clinical Studies, 261 from Janssen Supported Clinical Studies, and 1,536 from Post-marketing Sources (including spontaneous and solicited cases).

An overview of these cases is presented in Table 151 below.

Table 151: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting a Fatal Outcome

Case Characteristics		Number of Cases Received During the Reporting Period=1,269	Number of Cases Received Cumulatively=1,982
Sex	Female	506	819
	Male	607	939
	NR	156	224
Age (Years)[a]	0 to 17	4	4
Minimum: 4	18 to 35	84	137
Maximum: 100	36 to 50	173	287
Mean: 59.9	51 to 64	298	477
Median: 61	≥65	404	645
	Foetus	1	3
	Adult	3	8
	Elderly	9	10
	NR	293	411
Sources	Clinical study (interventional; non-solicited)	280	445
	Clinical study (non-interventional; solicited)	8	9
	Spontaneous	981	1528
Country/Territory[b]	United States	474	815
	Philippines	300	360
	South Africa	229	351
	Germany	39	73
	France	31	49
	Austria	18	22
	Brazil	18	30
	Greece	16	17
	Netherlands	15	26
	Italy	14	42
	Lesotho	14	20
	Estonia	10	10
	Argentina	9	12
	Czech Republic	7	8
	Lao People's Democratic Republic	7	7
	Poland	7	11
	Romania	6	6
	Spain	6	24
	Belgium	5	17
	Hungary	5	6
	Colombia	4	14
	Portugal	4	5
	Slovenia	4	5
	United Kingdom	4	6

Table 151: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting a Fatal Outcome

Case Characteristics	Number of Cases Received During the Reporting Period=1,269	Number of Cases Received Cumulatively=1,982

Key: NR=Not Reported.

a: The calculation is based on the current reporting period (25 August 2021 to 24 February 2022).

b: Countries/Territories with frequency ≥4 have been presented in decreasing order for the current reporting period (25 August 2021 to 24 February 2022).

The frequency distribution of top 15 fatal MedDRA PTs of interest reported in cases involving the use of Ad26.COV2.S is presented in Table 152 below. A single case may contain more than 1 EOI.

Table 152: Frequency Distribution of Top 15 Fatal MedDRA PTs Reported in Cases Involving the Use of Ad26.COV2.S

MedDRA PTs[a]	Number of Events Received During the Reporting Period[a]	Number of Events Received Cumulatively
Death	442	740
COVID-19	270	370
Dyspnoea	129	160
Pyrexia	104	132
Cough	91	106
Thrombosis	53	100
Malaise	45	64
COVID-19 pneumonia	42	64
Vaccination failure	42	47
Asthenia	41	56
Pulmonary embolism	40	75
Myocardial infarction	39	77
Suspected COVID-19	32	37
Fatigue	31	46
Cardiac arrest	28	59

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

a: The MedDRA PTs with frequency ≥28 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022). A single case may contain more than 1 EOI.

The frequency distribution of top 15 causes of death in cases reporting events with a fatal outcome involving the use of Ad26.COV2.S is presented in Table 153 below.

Table 153: Frequency Distribution of Top 15 Reported Causes of Death in Cases Reporting Events With a Fatal Outcome Involving the Use of Ad26.COV2.S

Cause of Death	Reported Causes Received During the Reporting Period[a]	Reported Causes Received Cumulatively
Death	432	689
COVID-19	210	300
Dyspnoea	119	137
Pyrexia	96	117

Table 153: Frequency Distribution of Top 15 Reported Causes of Death in Cases Reporting Events With a Fatal Outcome Involving the Use of Ad26.COV2.S

Cause of Death	Reported Causes Received During the Reporting Period[a]	Reported Causes Received Cumulatively
Cough	84	96
Thrombosis	46	88
COVID-19 pneumonia	40	64
Asthenia	36	44
Malaise	34	46
Myocardial infarction	31	65
Pulmonary embolism	30	56
Cerebrovascular accident	26	51
Decreased appetite	25	31
Cardiac arrest	23	48
Fatigue	22	33

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

a: The MedDRA PTs with frequency ≥22 have been presented by decreasing order for the reporting period (25 August 2021 to 24 February 2022).

Of these 1,269 cases, the duration between first administration of Ad26.COV2.S and fatal outcome was reported in 744 cases. The duration ranged from same day to 482 days (mean=86.8 days; median=43 days). In 573 cases, the latency of the fatal outcome was not reported.

Janssen Sponsored Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 102 cases reporting a fatal outcome were retrieved from Janssen Sponsored Clinical Studies. Of these cases, 76 were reported from VAC31518COV3001, 23 from VAC31518COV3009, and VAC31518COV2008, VAC31518COV1001, and VAC31518COV3005 (n=1 each) Of these 102 cases, the most frequently reported country/territory of origin was South Africa (n=43). Of the 102 cases, 70 concerned males and 32 females. The age range was 21 to 90 years.

The events with a fatal outcome (≥5) included death (n=21), and pneumonia and sudden death (n=6 each), and COVID-19 (n=5). The mean and median TTO for the events with fatal outcome was 245.8 days and 251 days, respectively. The Sponsor and Investigator's causality assessment of the EOI was reported as not related in all of the cases.

Janssen Supported Clinical Studies

During the reporting period of 25 August 2021 to 24 February 2022, 178 cases reporting a fatal outcome were retrieved from Janssen Supported Clinical Studies. Of these 178 cases, 172 were from VAC31518COV3012 (Sisonke) and were reported from South Africa. Of the 178 cases, 58 concerned males and 120 females. The age range was 29 to 81 years.

The events with a fatal outcome included COVID-19 (n=171), COVID-19 pneumonia (n=4), and headache, SARS-CoV-2 test positive, and sudden death (n=1 each). The mean and median TTO for the events with fatal outcome was 132.4 days and 127 days, respectively. Of these 178 fatal

events, The Company and Sponsor's causality assessment of the EOI was reported as related (n=1), as not related (n=176), and in the remaining event the Company causality was not reported, and the Sponsor causality was reported as not related.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During the reporting period of 25 August 2021 to 24 February 2022, 989 cases reporting a fatal outcome were retrieved from Post-marketing sources (including spontaneous and solicited cases). Of these 989 cases, the most frequently reported country/territory of origin was the US (n=450) followed by Philippines (n=292), and Germany (n=39). Of the 989 cases, 479 concerned males, 354 females, and 156 had no sex reported. The age range was 4 to 100 years.

The events (n≥25) with a fatal outcome included death (n=421), dyspnoea (n=128), pyrexia (n=103), COVID-19 (n=94), cough (n=91), thrombosis (n=53), malaise (n=45), vaccination failure (n=42), asthenia (n=41), pulmonary embolism (n=38), COVID-19 pneumonia (n=37), myocardial infarction (n=35), suspected COVID-19 (n=32), fatigue (n=31), decreased appetite (n=27), and cardiac arrest, and headache (n=25 each). The mean and median TTO was 75.3 days and 30 days, respectively.

Of the 989 post-marketing cases, 390 reported only the MedDRA PT of Death as a cause of death while 3 reported an unknown cause; hence, these cases were not associated with a specific safety concern.

COVID-19

A total of 383 cases reported an event related to COVID-19. The top 3 reported countries/territories of origin were South Africa (n=181), the US (n=101), and the Philippines (n=31). Of these 383 cases, 180 concerned males, 180 females, and 23 had no sex reported. The age range was 23 to 97 years with a median age of 59 years. Additional information can be found in Section 15.5, Vaccine Failure, Lack of Efficacy/Effectiveness.

Individual case safety report literature cases received during the reporting period were reviewed and upon review of the 14 cases including 4 cases with multiple patients, no information was identified that would raise a new specific safety concern.

Booster Dose

Cumulatively, 33 (8 medically confirmed and 25 medically unconfirmed) cases were identified reporting a fatal outcome in individuals who received the booster dose. Of these cases, 25 were homologous while 8 were heterologous. CIOMS II LL is presented in Appendix 7.31.

Conclusion

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

for the current reporting period, the analysis of fatal events has not raised any new safety concerns and the Company will continue to monitor the serious, life threatening, and fatal cases.

16.4. Characterisation of Risks

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 such as the Delta variant has fuelled the need for highly effective preventative measures. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S has demonstrated high efficacy against severe/critical disease caused by SARS-CoV2 and protection against hospitalisation and death. Recently available clinical data has also shown long persistence of the immune response as well as neutralising activity against the Delta and other variants of concern. Analysis of spontaneous reports of vaccination failure has not shown any trends of lack of efficacy.

The Company continues to monitor the new safety data available for Ad26.COV2.S vaccine and evaluates in real time the emerging safety data. The safety profile of the vaccine will be updated accordingly, and new safety data will continue to be presented in the upcoming SSRs.

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 44,105,710 million (CDC [2022], ECDC [2022], KDCA [2022]), available clinical trial data, as well as Real World Evidence (RWE) analyses (see Appendix 14). The Company considers, based on the data described in this PBRER, that Ad26.COV2.S vaccine continues to have a positive benefit-risk balance for the active immunisation to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age.

16.4.1. Characterisation of Important Identified Risks

The cRMP (version 4.0; dated 09 December 2021) was used as a reference for this section.

Anaphylaxis

Potential Mechanisms:

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. Anaphylaxis is triggered by the binding of allergens to specific Immunoglobulin E (IgE). It implies previous exposure and sensitisation to the triggering substance or a cross-reactive allergen. When an allergen binds to the IgE receptors on the surface of mast cells and basophils, this results in cellular activation and degranulation. These cells release preformed mediators such as histamine and tryptase that elicit the signs and symptoms of anaphylaxis. This mechanism is also known as the Type 1 immediate hypersensitivity reaction in the Gel and Coombs classification (Rüggeberg 2007).

"Anaphylactoid" reactions are clinically indistinguishable, but differ from anaphylaxis by their

immune mechanism, being characterised by mast cell activation due to a range of chemical or physical triggers independently of IgE. This mechanism is less well understood (Rüggeberg 2007).

Evidence Source(s) and Strength of Evidence:

Allergic reactions, including possibly severe reactions (eg, hypersensitivity reactions and anaphylaxis), are known to occur with any injectable vaccine. Ad26.COV2.S contains ingredients with known potential to cause allergic reactions, including polysorbate 80. The structure of polysorbate 80 presents similarities with polyethylene glycol, recently suspected to be involved in anaphylactic reactions with mRNA vaccines. The potential for polysorbate 80 to trigger hypersensitivity and the possibility of cross-reactivity between polyethylene glycol and polysorbate 80 have been discussed in the literature (Stone 2019a, Worm 2021). Cases of polysorbate 80 induced hypersensitivity have been reported and have involved different drugs, including a human papillomavirus vaccine (Badiu 2012), and different routes of administration, including the IM route.

Severe allergic reactions and 1 case of anaphylaxis have been identified following vaccination with Ad26.COV2.S in the context of clinical trials. All of these events occurred in the context of study COV3012 in South Africa, with the exception of a single SAE of Type IV (delayed) hypersensitivity from trial COV3001. Anaphylaxis is an ADR described in the CCDS.

Characterisation of the Risk:

In general, hypersensitivity reactions are a rare occurrence with Ad26-based vaccines. An update on the number of cases of anaphylaxis from clinical trial and post-marketing experience is provided in Section 16.3.1.1 of this PBRER.

Risk Factors and Risk Groups:

Participants with a known history of hypersensitivity to any component of the vaccine may be at risk for hypersensitivity reactions.

Preventability:

The CCDS (Section Contraindications) states that Ad26.COV2.S is contraindicated in individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or a severe allergic reaction after a dose of any other adenovirus-based vaccine. In addition, the CCDS (Section Warnings and Precautions) states that, as with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine. Individuals should be observed by a healthcare provider after vaccination based on clinical judgment.

Impact on the Risk-Benefit Balance of the Product:

Although anaphylactic reaction is a potentially life-threatening event requiring medical

intervention, the reporting frequency is very rare 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:

Anaphylaxis associated with vaccines typically occurs at a low incidence, resulting in a low public health impact. Although the potential clinical consequences of an anaphylactic reaction are serious, this is a risk known to healthcare professionals, with negligible public health impact.

Hypersensitivity reactions (serious and nonserious) were found to be rare during Ad26.COV2.S clinical development. Only 1 case of anaphylaxis (i.e., meeting the BC criteria) has been reported to date in clinical trials. Likewise, based on the case reports received from post-marketing experience, the occurrence of anaphylaxis following vaccination with Ad26.COV2.S is very rare.

Thrombosis with thrombocytopenia syndrome

Potential Mechanisms:

Thrombosis in combination with thrombocytopenia has been reported following vaccination with Ad26.COV2.S. Similar cases of TTS have also been described following administration of other COVID-19 vaccines, particularly with Vaxzevria, which uses a chimpanzee adenovirus (ChAdOx1) vector (Greinacher 2021, Schultz 2021). In literature discussion of the AEs, this phenomenon is referred to as VITT, which is also known as thrombosis with TTS. TTS following vaccination is characterised by the presence of IgG class platelet-activating antibodies directed against the cationic platelet chemokine PF4 (CXCL4), subsequently referred to as anti-PF4 antibodies Potential underlying mechanisms for a relationship between the induction of anti-PF4 antibodies and vaccination are currently unknown and are being explored.

A similar phenomenon of thrombosis and thrombocytopenia has also been reported following natural infection by SARS-CoV-2 (Brodard 2021), suggesting a role for the S protein is likely. However, recent studies suggest mechanisms may differ between natural infection and vaccination (Greinacher 2021).

With the planned 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 after vaccination.

Evidence Source(s) and Strength of Evidence:

Thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. A causal relationship with Ad26.COV2.S is considered plausible. TTS has been reported very rarely with another adenovectored COVID-19 vaccine, Vaxzeria. Cases have also been reported following vaccination with mRNA vaccines (Spikevax [Moderna] and Comirnaty [Pfizer-BioNTech]) (Sangli 2021,

Al-Maqbali 2021).

The background incidence rate of thrombosis in combination with thrombocytopenia ('combination' defined as thrombocytopenia occurring 10 days before or after thrombosis) was computed as part of the ACCESS project. Cases of thrombosis were categorized into 4 types, including venous thrombosis, arterial thrombosis, venous or arterial thrombosis, and CVST. The incidence rates for all 4 types, in combination with thrombocytopenia were extremely low, with rates estimated at 1/100,000 person-years (95% CI: 0.70-1.43); 1.46/100,000 person-years (95% CI: 1.09-1.96); 2.43/100,000 person-years (95% CI: 1.93-3.06), and 0.03/100,000 person-years (95% CI: 0.0-0.21) for venous, arterial, venous or arterial, and CVST, respectively. These events are likely to be observed in the hospital setting, therefore rates were extracted from a hospitalisation record linkage database, which also includes emergency room visits (ACCESS 2021).

Thrombosis in combination with thrombocytopenia is an ADR described in the CCDS.

Characterisation of the Risk:

While TTS is the AESI, it is a newly identified syndrome that may not have been encoded as such in clinical or post-marketing databases. Various case definitions currently exist (eg, interim BC case definition [Brighton Collaboration 2021], CDC working case definition [Shimabukuro 2021], and the case definition requested by PRAC, which is based on the case definition as proposed by the UK's NICE [NICE 2020]). An update on the number of cases of TTS from clinical trial and post marketing experience is provided in Section 16.3.1.2 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 <60 years.

Preventability:

The CCDS (Section Contraindications) states that Ad26.COV2.S is contraindicated in individuals with a history of confirmed TTS following vaccination with any COVID-19 vaccine. The CCDS (Warnings and Precautions) states that individuals who have experienced a previous CVST with thrombocytopenia or heparin-induced thrombocytopenia should only receive Ad26.COV2.S if the potential benefits outweigh the potential risks. Individuals who have experienced TTS following vaccination with any COVID-19 vaccine should not receive Ad26.COV2.S. The healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain or swelling, or progressive abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days,

should seek prompt medical attention. Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with Ad26.COV2.S should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

An initial direct healthcare professional communication (DHPC) has been provided to inform healthcare professionals to facilitate early detection/diagnosis and correct clinical management of TTS. The updated DHPC aims to reinforce the initial messages, in particular with regard to the required specialist clinical management of TTS. In addition, it emphasizes potential harms of heparin use for TTS patients and the need to investigate for other TTS symptoms following presentation with post-vaccination thrombosis or thrombocytopenia.

Impact on the Risk-Benefit Balance of the Product:

Thrombosis in combination with thrombocytopenia after vaccination with Ad26.COV2.S is a very rare event which is potentially life-threatening, especially if improperly managed. A causal relationship with Ad26.COV2.S is considered plausible. Adequate risk minimisation that raises public awareness and supports education of healthcare professionals may lead to earlier diagnosis and appropriate treatment, which may improve the prognosis of TTS. Natural infection with SARS-CoV-2 also carries a risk for thrombosis in combination with thrombocytopenia along with other complications (Makowski 2021, Wool 2021). Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

The occurrence of 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:

Guillain-Barré syndrome is a rare immune-mediated disorder of the peripheral nerves. Although its cause it not fully understood, the syndrome has been observed to follow viral or bacterial infection with *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein–Barr virus, measles, influenza A virus and *Mycoplasma pneumoniae*, enterovirus D68, Zika virus (Esposito 2017). More recently, GBS has been reported in association with SARS-CoV-2 infection (Sheikh 2021) where the absence of autoantibodies suggests a mechanistic pathway other than molecular mimicry typically associated with GBS secondary to infection (Freire 2021).

Since vaccines have an effect on the immune system it is biologically plausible that immunisations may be associated with subsequent GBS (Haber 2009). GBS has been linked in the past with certain vaccines, namely, rabies, polio and influenza (Stone 2019b), as well as hepatitis A and B, measles, mumps, rubella and varicella (MMR-V) (IOM 2012) and shingles (FDA 2021). Most

recently, cases of GBS have been reported following vaccination with COVID-19 vaccines, including mRNA and adenovectored vaccines (Razok 2021, Hasan 2021, Allen 2021). GBS has been reported as a very rare adverse event following immunisation (AEFI) with Ad26.COV2.S. No biological mechanism between GBS and Ad26.COV2.S has been established, although as with other vaccines, immune activation is believed to play an important role in the development of the disease.

Evidence Source(s) and Strength of Evidence:

GBS has been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and post-marketing setting. Similar AEs have also been described following administration of other COVID-19 vaccines. Despite no clear biological mechanism being identified, the Company considers the increase in O/E ratios since authorisation to be sufficient evidence for a plausible association between Ad26.COV2.S and GBS. GBS is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of GBS from clinical trial and post marketing experience is provided in Section 16.3.1.3 of this PBRER.

Risk Factors and Risk Groups:

Based mainly on data from North America and Europe, it has been shown in literature that the GBS incidence increased by 20% for every 10-year increase in age; GBS is usually more frequent in males, with the highest incidence between 50 to 70 years of age (Van Doorn 2020).

Approximately, a third of all GBS patients report symptoms of respiratory or gastrointestinal tract infection before the onset of GBS (Van den Berg 2014). Although many different infections have been identified in patients with GBS, case-control studies have revealed associations with only a few pathogens. *Campylobacter jejuni* is the most widely reported infection: it has been found in 25% to 50% of the adult GBS population and is more frequent in Asian countries. Other infections associated with GBS are those due to CMV, Epstein–Barr virus, measles, influenza A virus and *Mycoplasma pneumoniae*, as well as enterovirus D68 and Zika virus (Esposito 2017). More recently, GBS has been reported in association with SARS-CoV-2 infection (Sheikh 2021). GBS has been linked in the past with some vaccines, namely, rabies, polio, and influenza (Stone 2019b), as well as hepatitis A and B; measles, mumps, rubella and varicella (MMR-V) (IOM 2012); and shingles (FDA 2021). Most recently, cases of GBS have been reported following vaccination with COVID-19 vaccines, including mRNA and adenovectored vaccines (Razok 2021, Hasan 2021, Allen 2021).

Preventability:

The CCDS (Section, Warnings and Precautions) states that healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes.

Impact on the Risk-Benefit Balance of the Product:

Although GBS is a serious event that has been reported following vaccination with Ad26.COV2.S, it has been reported at a very low incidence and adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Therefore, the impact on the risk-benefit balance for the vaccine is considered to be low.

Public Health Impact:

GBS associated with vaccines typically occurs at a low incidence, resulting in a low public health impact. Although the potential clinical consequences of GBS are serious, this is a risk known to healthcare professionals, with negligible public health impact.

GBS was found to be very rare during Ad26.COV2.S clinical development. Only 3 cases of GBS have been reported to date in clinical trials following Ad26.COV2.S vaccination. Likewise, based on the case reports received from post-marketing experience (overall reporting rate of 4.6 per million patients fully vaccinated), the occurrence of GBS following vaccination with Ad26.COV2.S is very rare.

16.4.2. Characterisation of Important Potential Risks

CLS was removed from the list of safety concerns. CLS has not been reported during Ad26.COV2.S clinical development. Based on the case reports received from post-marketing experience (6 at the time of the DLP of 04 October 2021, from a total of more than 36 million administered doses of Ad26.COV2.S worldwide), the occurrence of CLS following vaccination with Ad26.COV2.S is extremely rare. The impact for public health is therefore assessed as minimal. The Company has reclassified CLS as an identified risk not considered important. The risk is well characterised and appropriate risk minimisation measures are included in the CCDS, where the Contraindications section states that Ad26.COV2.S is contraindicated in individuals with a history of CLS. There is no reasonable expectation that existing or future pharmacovigilance activities will provide further characterisation of the safety profile related to CLS.

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 favoring immunopathology) and antibody-mediated immune responses (antibody responses with insufficient neutralising activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells) (Graham 2020).

Evidence Source(s) and Strength of Evidence:

Based on past experiences in the development of vaccines against RSV, Dengue virus, SARS-CoV, and MERS-CoV, there is a theoretical risk for VAED, including VAERD, for

SARS-CoV-2 vaccines. As COVID-19 clinical manifestations are not limited to respiratory symptoms, not only VAERD, but also the broader term VAED is being taken into account.

VAERD was first seen in the 1960s in infants with RSV infection after receiving a vaccine against RSV that led to markedly worse respiratory disease as compared to non-vaccinated infants (Chin 1969, Fulginiti 1969, Kapikian 1969, Kim 1969). Subsequently, reports of VAED were reported in individuals without prior exposure to Dengue who received tetravalent Dengue vaccines (Su 2020). Nonclinical experience with SARS-CoV and MERS-CoV based vaccines (Agrawal 2016, Bolles 2011, Deming 2006, Honda-okubo 2015, Houser 2017) also indicated a risk for VAERD, however, this risk could not be confirmed in humans due to the lack of efficacy studies. To date there is no published evidence of VAED in nonclinical studies with IM SARS-CoV-2 vaccines. Furthermore, clinical trials with SARS-CoV-2 vaccines based on technologies other than the Ad26-vector platform, including the large-scale Phase 3 trials that are currently ongoing, have so far not reported any VAED either (Baden 2021, Polack 2020, Voysey 2021).

The observed VAERD in nonclinical studies with SARS-CoV and MERS-CoV based vaccines were attributed to induction of a Th2-skewed immune response. A Th1-skewed immune response as well as the induction of high levels of neutralising antibodies is considered desirable to prevent predisposition to enhanced respiratory disease as observed for RSV vaccines. It has been demonstrated in clinical trials that Ad26-based vaccines do induce humoral and strong cellular responses with a clear Th1 skewing (Anywaine 2019, Barouch 2018, Colby 2020, Milligan 2016, Mutua 2019, Stephenson 2020, Williams 2020). This type 1 skewing of the immune response is considered to minimise the risk of enhanced disease after SARS-CoV-2 infection.

Studies in Ad26.COV2.S immunised Syrian hamsters and nonhuman primate (NHP) conducted by the Company have shown the absence of enhanced lung pathology, absence of increased viral load, and absence of enhanced clinical signs of disease compared with controls after SARS-CoV-2 inoculation, even under conditions of suboptimal immunity allowing breakthrough infection (van der Lubbe 2021, He 2021). Together with induction of neutralising antibodies and a Th1-skewed immune response after Ad26.COV2.S dosing, these data suggest that the theoretical risk of VAERD and VAED for Ad26.COV2.S is low. These data were corroborated by the findings in clinical trials which have shown no indication of the presence of VAED, including VAERD.

Characterisation of the Risk:

An update on the number of cases of VAED/VAERD from clinical trial and post-marketing experience is provided in Section 16.3.2.1 of this PBRER.

Risk Factors and Risk Groups:

It is postulated that the potential risk may be increased in individuals producing lower neutralising

antibody titers or in those demonstrating waning immunity (Graham 2020, Munoz 2020).

Preventability:

An effective vaccine against COVID-19 that produces strong humoral and cellular immune responses with a clear Th1 bias is expected to mitigate the risk of VAED, including VAERD (Lambert 2020, Graham 2020). Such an immune profile is elicited by Ad26.COV2.S in clinical trials and nonclinical studies.

Impact on the Risk-Benefit Balance of the Product:

A confirmed risk of VAED, including VAERD could significantly impact the risk-benefit balance of Ad26.COV2.S. The risk will be further characterised through follow-up of study subjects in Phase 3 trials for the occurrence of severe COVID-19. Within post-authorisation effectiveness studies, the incidence of severe COVID-19 in vaccinated versus non-vaccinated populations will be used as an indirect measure of VAED, including VAERD.

Public Health Impact:

The potential risk of VAED, including VAERD could have a public health impact if large populations of individuals are affected.

Venous thromboembolism

Potential Mechanisms:

A potential mechanism for the occurrence of VTE includes a hypercoagulable state due to an excessive pro-inflammatory response to vaccination. Activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles can trigger the coagulation system through the induction of tissue factor (Branchford 2018). Vaccination with other viral vaccines such as those against influenza (Christian 2011, Tsai 2005) and human papillomavirus (Scheller 2014) have shown to cause a transient increase in pro-inflammatory cytokine production that may lead to the onset of VTE. This may also translate to other vaccines (Cruz-Tapias 2012, Mendoza-Pinto 2018). An underlying mechanism for VTE without thrombocytopenia has not been confirmed. Natural infection with SARS-CoV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and VTE or arterial thrombosis (Ribes 2020)

Evidence Source(s) and Strength of Evidence:

VTE has been observed rarely following vaccination with Ad26.COV2.S in clinical trials and in the post-marketing setting. While a higher proportion of cases of VTE was observed within the Ad26.COV2.S group versus the Placebo group in trial COV3001, there was no increase in VTE events among individuals who received Ad26.COV2.S in trial COV3009.

Characterisation of the Risk:

An update on the number of cases of VTE from clinical trial and post-marketing experience is provided in Section 16.3.2.2 of this PBRER.

Risk Factors and Risk Groups:

In the general population, important intrinsic factors for the onset of DVT and PE include a prior medical or family history of DVT or PE, venous insufficiency, heart disease, obesity, long periods of standing position, and multiparity. Important triggering factors for a DVT/PE event include pregnancy, trauma or a violent effort, deterioration of the general condition, immobilization, long distance travel, and infection (Samama 2000). On the other hand, CVST, including transverse sinus thrombosis (TST), is a disease more commonly observed in children and young adults. Important risk factors for CVST/TST include thrombophilia, trauma, puerperium, and chronic inflammatory diseases (Stam 2005). In addition, patients with CVST/TST have a strong risk for thrombosis, often misdiagnosed as idiopathic intracranial hypertension (Aldossary 2018). In trial COV3001, the following underlying risk factors have been identified in participants with VTE: male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, hypertension, and COPD. SARS-CoV-2 infection is also considered an important risk factor, with 46 participants (16 in the Ad26.COV2.S group, 17 in the Placebo group, 13 in the cross vaccinated group) having a positive PCR test.

Preventability:

The CCDS (Section Warning and Precautions) provides guidance to healthcare professionals to be alert to the signs and symptoms of thromboembolism.

Impact on the Risk-Benefit Balance of the Product:

VTE is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. VTE has been reported rarely following vaccination with Ad26.COV2.S. In the general population, VTE has an estimated frequency of 100 cases per 100,000 person-years. Adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of VTE events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

Immune thrombocytopenia

Potential Mechanisms:

ITP is an autoimmune bleeding disorder characterised by bleeding due to isolated thrombocytopenia with platelet count less than $100x10^9$ /L (Neunert 2011). Although most cases are asymptomatic, in rare instances ITP may be accompanied by severe bleeding, with cerebral bleeding being 1 of the most severe complications.

The biological mechanism linking Ad26.COV2.S and ITP is not fully known. ITP has been reported in the past with other vaccines, especially live viral vaccines (Di Pietrantonj 2020). ITP has also been described following administration of other COVID-19 vaccines, including mRNA and adenovector-based vaccines (Fueyo-Rodriguez 2021, Welsh 2021, Simpson 2021, Kuter 2021).

Although the exact mechanism of autoimmunity leading to ITP is still unclear, it is assumed that underlying mechanisms for ITP include an alteration of the balance between effector and regulatory immune cells. This imbalance results in a breakdown of the immune tolerance causing increased platelet clearance and impaired thrombopoiesis. Similar to other autoimmune disorders, molecular mimicry with bacterial or viral proteins might be one reason for the pathogenesis of ITP (Marini 2019).

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 16.3.2.3 of this PBRER.

Risk Factors and Risk Groups:

ITP is more common in young and middle-aged female adults, and more common in male children and older male adults (Moulis 2014). Adults are more likely to develop chronic ITP compared to children (Marini 2019). In patients with ITP, the occurrence of bleeding is strongly inversely correlated with platelet levels, with individuals with $<20x10^9$ /L being at a higher risk for bleeding (Piel-Julian 2018).

Limited data from post-marketing experience, including literature, with Ad26.COV2.S suggest that individuals with chronic or recurrent ITP may be at increased risk of developing ITP following vaccination with Ad26.COV2.S

Preventability:

The CCDS (Section Warnings and Precautions) states that if an individual has a history of ITP, the risk of developing low platelet levels should be considered before vaccination, and platelet monitoring is recommended after vaccination.

Impact on the Risk-Benefit Balance of the Product:

ITP is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. ITP has been reported very rarely following vaccination with Ad26.COV2.S. Based on current clinical trial and post-marketing data and the information in the CCDS, the risk-benefit balance for the vaccine is considered to remain favorable 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 in Pregnancy

Evidence source:

There is very limited experience with the use of Ad26.COV2.S in pregnant women.

Animal data from the EF-PPND toxicity study (TOX14389) with Ad26.COV2.S indicate no AE of Ad26.COV2.S on reproductive performance, fertility, ovarian and uterine examinations, or parturition. In addition, there was no AE of vaccination on foetal body weights, external, visceral and skeletal evaluations, or on post-natal development of the offspring.

Active vaccination of pregnant women has not been evaluated, as being pregnant or planning to become pregnant is an exclusion criterion in all clinical trials being conducted, with the requirement for use of adequate birth control methods for female subjects of childbearing potential. A pregnancy test is systematically being performed in these women before each study vaccine administration.

Up to the cut-off date of 31 December 2020, 8 pregnancies (4 in the Ad26.COV2.S group and 4 in the placebo group) were reported in the Company's safety database for trial COV3001. In 3 cases, vaccine exposure (Ad26.COV2.S or placebo) occurred within 3 months preceding the date of conception, with pregnancy outcomes reported as continuing/ongoing (n=2) or unknown/not reported (n=1). In 5 cases, vaccine exposure (Ad26.COV2.S or placebo) occurred during the first trimester of pregnancy, with pregnancy outcomes reported as continuing/ongoing (n=3), elective abortion (n=1), or spontaneous abortion (n=1, assessed as not related to blinded vaccine/placebo).

No additional pregnancies were reported between 31 December 2020 and 22 January 2021 (COV3001 CSR Feb 2021).

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 of this PBRER.

Safety data with other company Ad26-based vaccines when administered within 3 months before pregnancy as well as during pregnancy have shown no evidence of an increased risk of adverse outcomes in the mother or child in over 1,600 reported pregnancies, with over 900 reported pregnancy outcomes.

Anticipated risk/consequence of the missing information: Based on the non-replicating nature of the vaccine and on nonclinical and very limited clinical and post-marketing data available to date, including data on the use of other Ad26-based vaccines during pregnancy, the safety profile of Ad26.COV2.S when used in pregnant women is not expected to differ from that in the general population, with no specific safety concerns for pregnant women or foetuses to date. Therefore, as stated in the CCDS (Section Pregnancy, Breastfeeding and Fertility), the administration of Ad26.COV2.S in pregnancy may be considered when the potential benefits outweigh any potential risks to the mother and fetus.

A Phase 2 trial (COV2004) and a post-authorisation pregnancy exposure registry (COV4005) will assess the safety and immunogenicity of Ad26.COV2.S in pregnant women and their offspring

Use in Breastfeeding women:

Evidence Source:

Breastfeeding women were excluded from all clinical trials, except from the Phase 3 trials COV3001 and COV3009. Up to the 04 October 2021, 239 breastfeeding women who were breastfeeding at baseline have received Ad26.COV2.S in trial COV3001, and approximately 110 breastfeeding women who were breastfeeding at baseline have received Ad26.COV2.S in trial COV3009. No data to assess the safety profile are currently available in this subpopulation and the risk in this population has not yet been defined. Approximately 1,042 breastfeeding women have received the Company's Ad26-based Ebola vaccine in a clinical trial in Democratic Republic of the Congo. Up to 30 June 2021, there have been 37 cases (post-marketing spontaneous or non-interventional cases) of exposure to Ad26.COV2.S vaccine via breastfeeding. No abnormal trend was observed. Currently, there is no evidence of SARS-CoV-2 transmission through breast milk. Limited data on breastfeeding women with active SARS-CoV-2 infection showed limited excretion of viral particles but no live virus in breastmilk (Centeno-Tablante 2021). In addition, several reports suggest the presence of secretory IgA against SARS-CoV-2 S protein in breast milk from donors with prior COVID-19 (Fox 2020, Dong 2020, Demers-Mathieu 2020).

It is not known whether the components of Ad26.COV2.S or the antibodies induced by Ad26.COV2.S are excreted in human milk. Human data are not available to assess the impact of Ad26.COV2.S on milk production or its effects on the breastfed child.

Anticipated risk/consequence of the missing information

No effects on the breastfed child are anticipated considering results from animal and human studies with Ad26-based vaccines, showing limited dissemination of this nonreplicating 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 subjects within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk.

Use in Immunocompromised Patients

Evidence source:

Patients with stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 (e.g., stable/well-controlled HIV infection), or those receiving chronic low-dose (less than 20 mg of prednisone or equivalent) immunosuppressive therapy were not excluded from trials COV3001 and COV3009.

In trial COV3009, 386 subjects who received at least 1 dose of Ad26.COV2.S had a stable/well-controlled HIV infection.

In trial COV3001, 601 (2.7%) subjects in the final analyses set (FAS) and 34 (1.0%) subjects in the Safety Subset who received Ad26.COV2.S had a stable/well-controlled HIV infection. Subjects with other immunodeficiencies were included at very low numbers, not allowing to provide meaningful data (COV3001 CSR Feb 2021).

Ad26.COV2.S has not been assessed in immunocompromised individuals including those receiving immunosuppressant therapy. These individuals may have a diminished immune response to Ad26.COV2.S.

Based on the primary analysis results from trial COV3001, no conclusion could currently be made about VE in HIV-infected subjects. In this subpopulation, the number of moderate to severe/critical COVID-19 cases was too small to draw efficacy conclusions but the results did not suggest a negative impact of the vaccine. Additional and longer follow-up time for case accrual data will be gathered as the trial continues to better understand observed data. No clinically relevant difference in the reactogenicity profile could be observed in HIV infected versus HIV negative subjects.

In the FAS of trial COV3001, SAEs were reported in 4 (0.7%) out of 601 HIV-infected subjects

who received Ad26.COV2.S, of which none were considered to be related to the study vaccine by the investigator. The frequency of reported SAEs was similar in the Ad26.COV2.S and placebo groups.

An update on the number of cases from clinical trial and post-marketing experience in immunocompromised patients is provided in Section 16.3.5.3 of this PBRER.

Anticipated risk/consequence of the missing information:

Given the fact that Ad26.COV2.S is a replication-incompetent vaccine, the safety profile of Ad26.COV2.S when used in immunocompromised individuals is not expected to differ from that in the general population, with no specific safety concerns. This was confirmed by clinical trial data with Ad26.ZEBOV, for which the safety and immunogenicity was assessed in HIV infected adults with infection controlled through antiretroviral therapy. In these trials, there were no specific safety concerns and no notable differences between HIV infected and healthy subjects with regard to reporting frequency or severity of AEs at any timepoint. The limited safety data available from trial COV3001 are comparable to the findings with Ad26.ZEBOV.

Use in immunocompromised patients will be further characterised in an interventional trial and in the post-authorisation safety studies COV4003 and COV4001 and effectiveness studies COV4004 and COV4002 with Ad26.COV2.S.

Use in Patients With Autoimmune or Inflammatory Disorders

Evidence source:

There is limited information on the safety of Ad26.COV2.S in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Subjects with clinical conditions stable under non-immunomodulator treatment (e.g., autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could be enrolled in Phase 3 trials COV3001 and COV3009 at the discretion of the investigator.

An update on the number of cases from clinical trial and post-marketing experience in patients with autoimmune or inflammatory disorders is provided in Section 16.3.5.4 of this PBRER.

Population in need of further characterisation:

Use in patients with autoimmune or inflammatory disorders will be further characterised in the post-authorisation safety studies COV4003 and COV4001 with Ad26.COV2.S.

Use in Frail Patients With Comorbidities (e.g., Chronic Obstructive Pulmonary Disease [COPD], Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Evidence source:

Frail individuals, especially those with multiple comorbidities that may compromise their immune response, are at an increased risk for severe COVID-19. In addition, the safety profile in this subpopulation could vary from that seen in healthy adults. Increased age and comorbidities are the 2 major risk factors for frailty.

Of the 8,936 subjects in the FAS of trial COV3001 who received Ad26.COV2.S and had 1 or more comorbidities, 3,704 (41.5%) were aged ≥60 years, 2,271 (25.4%) were aged ≥65 years, and 495 (5.5%) were aged ≥75 years. The proportion of these subjects that have been determined to be frail is currently unknown (COV3001 CSR Feb 2021).

There is limited information on the safety of Ad26.COV2.S in frail patients with comorbidities that may compromise their immune response.

Following a protocol amendment for trial COV3001 on 14 December 2020, calculation of a frailty index has been included to be applied to subjects enrolled, but these data are not available as part of the primary analysis of this trial.

An update on the number of cases from clinical trial and post-marketing experience in frail patients with comorbidities is provided in Section 16.3.5.5 of this PBRER.

Population in need of further characterisation:

Safety data will be collected in individuals who are frail due to age or debilitating disease in trial COV3001, in the post-authorisation safety studies COV4003 and COV4001 with Ad26.COV2.S, in the post-authorisation effectiveness study COV4002 with Ad26.COV2.S, and through routine PV.

Interaction With Other Vaccines

Evidence source:

As no interaction studies have been performed, there are no data to assess if concomitant administration of Ad26.COV2.S with other vaccines may affect the efficacy or safety of either vaccine. This also applies to mixed schedules with other COVID-19 vaccines.

An update on the number of cases from clinical trial and post-marketing experience in cases with interaction with other vaccines is provided in Section 15.3 of this PBRER.

Population in need of further characterisation:

All reports describing interactions of Ad26.COV2.S with other vaccines per national

recommendations will be collected and analysed as per routine pharmacovigilance activities. A coadministration study of Ad26.COV2.S with seasonal influenza vaccine is planned.

Long term Safety

Evidence source:

There are no available data on the long term safety of Ad26.COV2.S.

Based on long term safety data from other Ad26-based vaccines (at least 6 months up to 4.5 years post-vaccination in clinical trials), no long term safety issues have been identified (Adenoviral Vaccine Safety Database V5.0 2020).

An update on the number of long term safety cases is provided in Section 16.3.5.7 of this PBRER.

Population in need of further characterisation:

At the time of vaccine availability, the long term safety of Ad26.COV2.S will not be fully known; however, there are no known risks with a potentially late onset based on the available evidence with other Ad26-based vaccines.

Long term safety data are being collected for at least 2 years in ongoing trials COV3001 and COV3009 following administration of Ad26.COV2.S, and for up to 1 year in the post-authorisation safety studies COV4003 and COV4001 with Ad26.COV2.S.

Subjects of trials COV3001 and COV3009 who initially received placebo are being unblinded and offered a single dose of Ad26.COV2.S (crossover vaccination), since the vaccine has received an EUA in the US and conditional Marketing Authorisation in the EU/EEA. All subjects will be encouraged to remain in the trial and will be followed for safety as originally planned up to 2 years after vaccination.

16.5. Effectiveness of Risk Minimisation

No significant new information on the effectiveness or limitations of specific risk minimisation activities for the important identified risk or important potential risk has become available during the reporting period for Ad26.COV2.S.

17. BENEFIT EVALUATION

As of 31 August 2021, there have been 216,867,420 confirmed cases of COVID-19 globally, including 4,507,837 deaths. As of 30 August 2021, a total of 5,019,907,027 vaccine doses have been administered (WHO 2021).

In the US, as of 31 August 2021, there have been a total of 38,666,040 confirmed cases of COVID-19 reported, and 632,983 cases of COVID-19 related deaths reported. A total of 367,316,149 vaccine doses have been administered (WHO 2021).

Over the course of the SARS-CoV-2 pandemic, changes in SARS-CoV-2 occurred. Some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures. WHO (WHO 2021a, CDC 2021a), in collaboration with partners, expert networks, national authorities, institutions and researchers have been monitoring and assessing the evolution of SARS-CoV-2 since January 2020. During late 2020, the emergence of variants in several countries, such as UK, RSA, Brazil, India, US, Peru, Columbia that posed an increased risk to global public health prompted the characterisation of specific Variants of Concern (VOCs), and Variants of Interest (VOIs) to prioritize global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic. Currently, VOCs are Alpha (B.1.1.7, earliest detection: UK), Beta (B.1.351, earliest detection: RSA), Delta (B.1.617.2, earliest detection: India), Gamma (P.1, earliest detection: Brazil). VOIs are Eta (B. 1.525; earliest detection in several countries), Iota (B.1.526, earliest detection: US), Kappa (B. 1.617.1, earliest detection: India), Lambda (C.37, earliest detection: Peru), and Mu (B.1.621, earliest detection: Colombia.

The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their increased transmission rates, more severe disease (increased hospitalisations or deaths), and because of the possibility that current COVID-19 vaccines authorized under EUA 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

Information on baseline efficacy/effectiveness on COV3001 can be found under the key benefits subsection of Section 18.2 Benefit- Risk Analysis Evaluation.

Vaccine Efficacy Against Severe/Critical COVID-19, COVID-19 related Hospitalisations/Deaths

Vaccine efficacy against severe/critical COVID-19 remained higher than against moderate to severe/critical COVID-19.

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. Vaccine efficacy against severe/critical COVID-19 was consistent across age groups, participants without/with comorbidities, regions, countries and against SARS-CoV-2 variants with sufficient cases, including the Beta, Gamma VOCs and Lambda, Mu VOIs (as discussed below). VE estimates (adjusted 95% CI) against severe/critical COVID-19 in the primary analysis were 76.7% (54.56; 89.09) and 85.4% (54.15; 96.90), respectively. VE estimates (adjusted 95% CI) in prevention of 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.

Vaccine Efficacy Against SARS-CoV-2 VOCs/VOIs

When considering the vaccine efficacy 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 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 vaccine efficacy against this VOC. Similarly, for the Alpha VOC there were 2 versus 4 severe/critical cases in the Ad26.COV2.S group versus the placebo group, not allowing to draw meaningful conclusions for severe COVID-19 caused by this variant.

Generally, there was continued protection against severe/critical COVID-19 for SARS-CoV-2 variants, including Beta, Gamma VOCs (64%, 78%), Lambda, Mu VOIs (67%, 80%).

Differences were observed in protection against moderate to severe/critical COVID 19 among the SARS-CoV-2 variants including VOCs/VOIs (range VE estimates 10%-70%). No reduction in VE estimates compared to that of the reference strain (VE estimate [95%CI] 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<36%) The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). These findings potentially contribute to the observed reduction in protection against moderate to severe/critical COVID-19 since the primary analysis, however waning protection cannot be excluded.

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

When considering the vaccine efficacy (VE) against SARS-CoV-2 variants, including VOCs/VOIs, observed in the trial, COV3001, caution is needed when interpreting data where there

were (too) few COVID-19 cases and/or confidence intervals (CIs) were wide. Differences were observed in protection against moderate to severe/critical COVID-19. No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI]: 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants was observed, while the VE estimates for the Delta, Gamma VOCs, Mu, and 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% and 91% across variants with sufficient COVID-19 cases, such as Beta, Gamma VOCs, Lambda, and 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, the 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 VOC in a real world setting.

In addition to this clinical efficacy studies, the Company has conducted a review during the reporting period of the currently available real-world evidence (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 summarized below. The full report is available in Appendix 14.

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 (5x1010 vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US. HealthVerity COVID-19 data consists of longitudinal, de-identified patient-level real-world data for approximately 160M patient lives submitted by US providers of inpatient, outpatient, pharmacy, and laboratory services from 01 March 2021 to 31 August 2021 from open-source medical claims data aggregated by HealthVerity. Overall, the results of the interim analysis indicate that a single dose of Ad26.COV2.S protects against observed COVID-19 and COVID-19-related hospitalisation in the real-world setting and that the vaccine efficacy 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.

Sisonke is a Phase 3B, open-label, implementation study of VE of Ad26.COV2.S in healthcare workers (HCW) sponsored by the South African Medical Research Council (SAMRC) in South Africa which commenced on 17 February 2021 and ended on 16 May 2021 (Bekker 2021). This

study focused on HCWs aged >18 years of age with SARS-CoV-2 test results collected by the National Institute for Communicable Diseases (NICD) in the COVID-19 notifiable medical conditions sentinel surveillance (NMCSS) system. While not explicitly deriving VE against infection and hospitalisation, differences were noted between Beta and Delta breakthrough infection (BTI) patterns in SISONKE HCWs, with Delta producing a higher proportion of hospitalisations in individuals between 31 to 54 years of age (60%) than Beta (51%) (Goga 2021). Although a higher proportion of HCWs required general ward care during the Delta period compared to the Beta period (89% and 78%, respectively), fewer HCWs required high or intensive care (4% and 7% during Delta compared to 7% and 16% during Beta).

Results of additional RWE studies that report Ad.26.COV2S effectiveness have recently been reported. These studies investigated the RWE of Ad26.COV2.S for prevention of COVID-19, hospitalisation and death using electronic health records from multi-state health systems, networks, and hospitals. These studies focus on individuals who received a single dose of the Ad26.COV2.S vaccine with comparison to control groups following local regulatory approval. Results were reported across different geographies, age categories, ambulatory, and inpatient care settings. In some reports, comparative effectiveness of Janssen, Moderna and Pfizer-BioNTech vaccines were reported on; however, this summary focuses on the VE of Ad26.COV2.S. Despite these limitations, results from many of the studies (Bekker 2021,Corchado-Garcia 2021, Moline 2021, de Gier 2021) are consistent with the vaccine effectiveness seen with the single-dose Ad26.COV2.S vaccine in COV4002.

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 program is an accelerated development program that was designed specifically to address the COVID-19 pandemic. Despite the present availability of vaccines authorised for cMA and EUA (and 1 licensed in the US), 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 emergency

of new variants highlights the need to continue primary vaccination. A 1-dose regimen and favorable storage conditions are advantages conferred by the Ad26.COV2.S vaccine in protecting against COVID-19 infection caused by the SARS-CoV-2 virus, which are particularly important for immunizing hard-to-reach populations.

Over the course of the SARS-CoV-2 pandemic, several new SARS-CoV-2 variants of concern emerged in the UK (B.1.1.7 lineage [alpha]), in Brazil (P.1 lineage [gamma]), in the Republic of South Africa (B.1.351 lineage [beta]), and in India (B.1.617 lineage [delta]) and new variants of interest (e.g., B.1.427/B.1.429 lineage [CAL.20, epsilon] in California) continue to emerge, which may spread globally. The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their increased transmission rates, more severe disease (increased hospitalisations or deaths), and because of the possibility that current COVID-19 vaccines authorised under EUA 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 neutralized 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 16 July 2021, there have been 188,655,968 confirmed cases of COVID-19, including 4,067,517 deaths worldwide (WHO 2021). In the EU/EEA, as of Week 2021-33, starting 16 August 2021 (based on cumulative data from 11 March 2021), there have been a total of 36,307,572 confirmed cases of COVID-19 reported, and 750,921 cases of COVID-19 related deaths reported (ECDC 2021).

Respiratory symptoms of COVID-19 typically appear 5 to 6 days following exposure to the virus, with the clinical manifestations ranging from mild symptoms to severe illness or death (CDC 2020a; Guan 2020; Linton 2020; US San Diego Health 2020; WHO 2020), including signs and symptoms of respiratory distress such as blue lips, extreme shortness of breath and dyspnea, persistent cough, deep vein thrombosis, discoloration of feet and toes, chills, shaking chills, loss of sense of taste and smell, signs of stroke, disorientation, inability to respond or understand verbal communication, among others. Other less common gastrointestinal symptoms have been reported by CDC (nausea, vomiting, diarrhea) (CDC 2020a).

At present, it appears that individuals aged 65 years or older, especially those with comorbidities, such as cancer, cardiovascular disease, Type 2 diabetes mellitus, (severe) obesity, hypertension, chronic kidney disease and underlying pulmonary disease, are subject to the highest incidence of morbidity and mortality (CDC 2020b; Garg 2020; Luo 2020; Verity 2020). 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 4 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.

The pivotal Phase 3 Ad26.COV2.S efficacy and safety study COV3001 was initiated shortly before the incidence of COVID-19 increased substantially across the globe. This was reflected in an estimated COVID-19 incidence rate in the study of 19.8%. There is evidence that vaccine efficacy, as commonly estimated in randomized clinical studies, decreases with increasing disease incidence (Gomes 2016). The time of study conduct also coincided with the emergence of new SARS-CoV-2 variants, which were also emerging in some of the countries where COV3001 is being performed. The setting of the COV3001 study allowed to study VE against COVID-19 caused by different SARS-CoV-2 variants as well as VE against COVID-19 early after vaccination in a situation of very high SARS-CoV-2 transmission rates.

Primary Efficacy Endpoints

A single dose of Ad26.COV2.S protects against COVID-19 in adults ≥18 years of age, including adults ≥60 years of age. 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 Against Severe/Critical

COVID-19 Vaccine efficacy against severe/critical COVID-19 was higher than against moderate COVID-19. 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, regions and countries.

Vaccine Efficacy Over Time

Vaccine efficacy increases over time, especially the vaccine efficacy against severe/critical COVID-19. The onset of efficacy against moderate to severe/critical COVID-19 was evident as of 14 days after a single Ad26.COV2.S dose, which persisted for the current duration of follow-up (median 58 days). The onset of efficacy against severe/critical COVID-19 was evident as early as of 7 days after a single dose, with a clear trend for increasing vaccine efficacy which persisted for the current duration of follow-up (median 58 days). Of note, after Day 42, only 1 confirmed severe/critical COVID-19 case was reported in the Ad26.COV2.S group (on Day 48) while

13 cases were reported in the placebo group. This is consistent with available immunogenicity results from Phase 1/2a, which show that, following a single dose of Ad26.COV2.S, neutralizing and binding antibody titers were detected from Day 15 and increased from Day 29 through Day 57 with no indication of rapid waning up to Day 85. The durability of immunogenicity and efficacy are being evaluated in COV3001 and supporting studies.

Vaccine Efficacy Against All Symptomatic COVID-19

Vaccine efficacy (adjusted 95% CI) against all symptomatic COVID-19, as measured by a severity-adjusted analysis (BOD) including mild, moderate and severe/critical disease, occurring at least 14 days and at least 28 days after a single Ad26.COV2.S dose was 68.1% (60.26; 74.32) and 69.0% (56.68; 77.64), respectively. Given the increased vaccine efficacy against severe/critical COVID-19, the severity-adjusted vaccine efficacy against all symptomatic COVID-19 was slightly higher compared to the unweighted vaccine efficacy against any symptomatic COVID-19 (66.9% [59.07; 73.37] and 66.5% [55.50; 75.05], as of 14 and 28 days after vaccination, respectively).

Vaccine Efficacy in Subgroups

Results for VE against moderate to severe/critical COVID-19 and for VE against severe/critical COVID-19 from supplementary analyses taking into consideration all COVID-19 cases with at least 1 positive PCR result regardless of confirmation at the central laboratory, are in line with results from analyses only taking molecularly confirmed cases at the central laboratory into account. Therefore, to allow for the largest possible dataset, subgroup analyses described in these paragraphs are based on all COVID-19 cases with at least 1 positive PCR result regardless of confirmation at the central laboratory. As the proportion of participants in certain subgroups are low, the number of participant years of follow-up is small, resulting in low case accrual in these subgroups. The uncertainty on the VE estimates are reflected by the wide CI and results should be interpreted with caution for those.

Vaccine efficacy against moderate to severe/critical COVID-19 and against severe/critical COVID-19 after a single dose of Ad26.COV2.S was evaluated for the following subgroups: age, comorbidities, sex, country/region, race, ethnicity, age and comorbidities, baseline SARS-CoV-2 serostatus, and HIV infection status. For the subgroups where sufficient data are available to allow efficacy estimation (age, comorbidities, sex, some of the countries, regions, race, and ethnicity), further detail is provided in the next paragraphs. Additional and longer follow-up time for case accrual data will be gathered as the study continues to better understand observed data for the other subgroups (age and comorbidities, some of the countries, baseline SARS-CoV-2 serostatus, and HIV infection status). As the study continues, case accrual will continue and may allow for a better characterisation and understanding of potential differences between subgroups at the time of a subsequent analysis.

Ad26.COV2.S is efficacious across age groups (≥60 years and ≥18 years to <60 years to with estimated VEs against moderate to severe/critical COVID-19 of at least 65.0% and at least 60.4%

as of 14 days and 28 days after vaccination, respectively and VE across age groups against severe/critical COVID-19 of at least 75.1% and at least 80.2% as of 14 days and 28 days after vaccination, respectively.

The VE against moderate to severe/critical COVID-19 occurring at least 14 and at least 28 days after vaccination was 67.6% (59.38; 74.30) and 68.8% (58.98; 76.58), respectively, in participants without comorbidities and 64.2% (52.68, 73.14) and 58.6% (40.57; 71.55), respectively, in participants with comorbidities. VE against severe/critical COVID-19 was ≥75.6% as of 14 days after vaccination and ≥75.2% as of 28 days after vaccination, irrespective of the presence of comorbidities. There were fewer participants with co-morbidities than without co-morbidities (N <7,800 vs >11,500), resulting in a lower number of person-years (approximately 1,100 vs approximately 2,000) for case accrual in the subgroup of participants with comorbidities.

Participants ≥60 years of age without comorbidities had a higher VE estimate than participants ≥60 years of age with comorbidities. Next to the difference in number of participants, another factor potentially driving the observed difference could be the length of follow-up after vaccination. Per protocol design, vaccination of participants with comorbidities could start only after safety review of 2,000 participants without comorbidities. Therefore, the participants with comorbidities have a shorter follow-up time. The Kaplan Meier curves and plots of VE estimates over time suggest an increase in protection up to 50 to 60 days after immunisation. If, as presumed, this observation is related to the status of maturity of the immune responses, differences in follow-up time upon exposure may be reflected in differences in VE between populations. More follow-up data will be gathered as the study continues to understand observed potential differences between these subgroups.

Ad26.COV2.S VE was consistent between sexes, between Hispanics and non-Hispanics, and between Black/African Americans and Whites. For some of the other racial groups, the findings were variable and therefore, additional and longer follow-up time for case accrual data will be gathered as the study continues to understand observations in some of the races. Across regions, VE against moderate to severe/critical COVID-19 with onset at least 14 days and at least 28 days after vaccination VE ranged from 52.0% to 74.4%.

Vaccine Efficacy Against Newly Emerging SARS-CoV-2 Strains

In the US, vaccine efficacy against moderate to severe/critical COVID-19 was 74.4% and 72.0%, when considering cases from at least 14 days and at least 28 days after vaccination, respectively. Vaccine efficacy (95% CI) against severe/critical COVID-19 in the US was 78.0% as of day 15 and 85.9% as of day 29 post-vaccination. Preliminary sequence data confirm that approximately 96% of these COVID-19 cases were due to the D614G variant and approximately 3% were due to the CAL.20C (epsilon) variant.

In South Africa, high efficacy was observed against severe/critical COVID-19 and robust vaccine efficacy was observed for moderate to severe/critical COVID-19. Preliminary sequence data confirm that approximately 96% of the COVID-19 cases that occurred in the study in South Africa

were due to the SARS-CoV-2 strain variant 20H/501Y.V2 (belonging to the B.1.351 lineage), implying that Ad26.COV2.S is efficacious against this strain, which was newly emerging and rapidly spreading at the time of the primary analysis. Vaccine efficacy (95% CI) against severe/critical COVID-19 was 73.1% as of day 15 and increased to 81.7% as of day 29 post-vaccination. An effect was also seen on mortality, since all COVID-19-related deaths in the study, were in the placebo group. Vaccine efficacy (95% CI) against moderate to severe/critical COVID-19 was 52.0% as of Day 15 and 64.0% as of day 29 post-vaccination.

In Brazil, were approximately 70% of the COVID-19 cases were due to a variant from the P.2 lineage, vaccine efficacy estimates were higher than those in South Africa and similar to those in the US.

Reduction in COVID-19 Symptoms

Participants with moderate COVID-19 in the Ad26.COV2.S group experienced fewer symptoms than in the placebo group. Furthermore, the daily average symptom severity score (total Symptoms of Infection with Coronavirus-19 [SIC] score) of moderate COVID-19 cases with onset at least 14 and 28 days after vaccination as reported by participants was lower in participants with moderate COVID 19 in the Ad26.COV2.S group compared to the placebo group, during the COVID-19 episode.

Immunogenicity

A single dose of Ad26.COV2.S elicits both humoral and cellular immune responses in adult participants ≥18 to ≤55 years and ≥65 years of age. Across the Phase 1 and 2 studies, Ad26.COV2.S elicited a SARS-CoV-2 neutralizing antibody response in at least 83% and 88% of participants ≥18 to ≤55 years and at least 71% and 93% of participants ≥65 years of age at day 15 and day 29, respectively. Similarly, Ad26.COV2.S elicited a SARS-CoV-2 Spike-binding antibody response in at least 99% of participants ≥18 to ≤55 years at Day 29[17] and 73% and 95% of participants ≥65 years of age at day 15 and day 29, respectively. In study COV1001, Ad26.COV2.S elicited CD4 and CD8 T cell responses in participants ≥18 to ≤55 years and participants ≥65 years of age, by day 15 and up to 28 days after a single dose. All measurable CD4 T cell responses were predominantly of the Th1 phenotype.

In participants ≥18 to ≤55 years of age, neutralizing and binding antibody responses increased from day 29 to day 57 and were maintained up to at least day 85 in study COV1001. In participants ≥65 years of age, neutralising and binding antibody responses were maintained from day 29 up to at least day 87. For both age groups, later timepoints are being evaluated. This finding is consistent with durability of immune response observed with the Ad26-vector platform data. Similar to immune response kinetics observed in humans, NHP showed increasing neutralizing antibody responses up to day 29 post single dose immunisation with 5 x1010 vp Ad26.COV2.S, that were

[17] No Day 15 humoral immunogenicity data are available for participants ≥18 to ≤55 years of age.

measured to be stable up to Day 99. Binding antibody titers peaked at day 29, showed a limited decline up to day 99 when a stable plateau was reached and maintained until Day 183. Relevance of the durable immunity was confirmed in NHP challenged with SARS-CoV-2 at 6 months post single Ad26.COV2.S immunisation as these showed undetectable lung viral loads in 13 of 14 animals (Roozendaal 2021).

Overall Assessment of Benefit Ad26.COV2.S (COVID-19 Vaccine Janssen) is efficacious, elicits a durable humoral and cellular immune response, has favorable storage conditions, and only requires administration of a single dose, which simplifies deployment of the vaccine.

The long-term and robust platform data demonstrate an acceptable safety and reactogenicity profile and durable immune responses for the Ad26-based vaccines. Therefore, Ad26.COV2.S remains a valuable and relevant asset to address the COVID-19 pandemic.

Key Risks

The safety concerns from the cRMP are provided below:

Safety concerns at the start of the PBRER reporting period

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

During the reporting period, CLS was removed from the list of safety concerns.

Overall Assessment of Risk

The initial safety profile of Ad26.COV2.S vaccine was established at the time of first authorisation (at the start of the reporting period) based on the interim analysis from the pivotal Phase 3 Ad26.COV2.S efficacy and safety study COV3001, complemented by blinded safety data from then ongoing Phase 1/2 and 3 studies. Since then, additional information became available through routine safety pharmacovigilance activities (such as signal detection) for which the results were reflected in updates of the RMP, the monthly MSSRs, and amendments to the CCDS.

A single dose of Ad26.COV2.S has an acceptable safety and reactogenicity profile in adults

≥18 years of age, including adults ≥60 years of age. In general, lower reactogenicity was observed in older adults compared to younger adults. The most frequently reported solicited (local and systemic) AEs (collected up to 7 days after vaccination in the Safety Subset) after a single dose of Ad26.COV2.S 5×1010 vp were vaccination site pain, fatigue, headache, and myalgia. Most AEs were of mild or moderate severity, were transient in nature and generally resolved within 1 to 2 days post-vaccination.

The most frequently reported unsolicited AEs (collected up to 28 days after vaccination in the Safety Subset) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs by PT, not recorded as solicited AEs, were chills, nasal congestion, arthralgia, cough, and diarrhea. Most were of mild or moderate severity and most were considered not related to the study vaccine by the investigator. The overall frequency of SAEs was low and balanced between placebo and active groups.

Post-marketing experience with Ad26.COV2.S has demonstrated a similar safety profile to that observed in clinical trials. Serious adverse reactions observed in the post-marketing experience including TTS, GBS, ITP, and VTE occurred very infrequently, are adequately monitored, and do not outweigh the significant benefits of single-dose vaccination with Ad26.COV2.S. The current post-authorisation exposure insufficient to establish differences in the onset and severity of these very rare ADRs between primary and booster usage of Ad26.COV2.S.

Integrated Benefit-Risk Evaluation Conclusions

Despite increasing numbers of vaccinated subjects, the ongoing SARS-CoV-2 pandemic remains a public health issue of international concern. The emergence of new virulent lineages has fuelled the need for highly effective preventative 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. Booster usage (homologous or heterologous) has shown significant increase in vaccine efficacy in the long-term and against emerging variants.

As of 24 February 2022, over 44,105,710 million doses of the Ad26.COV2.S vaccine have been administered (CDC 2022, ECDC 2022, KDCA 2022). Increasing experience based on spontaneous/solicited post-marketing reporting of adverse events, have led to the identification of new, some serious, adverse events/reactions such as TTS, GBS, and ITP). These risks occur very infrequently, are adequately monitored and do not outweigh the significant benefits of single-dose vaccination with Ad26.COV2.S in controlling the global pandemic. Potential safety concerns will continue to be monitored.

Taking into account the safety data cumulatively, as well as the late breaking information, the

overall benefit-risk assessment remains favourable for Ad26.COV2.S when used as recommended in the currently approved indications for both primary and booster active immunisation to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age.

19. CONCLUSIONS AND ACTIONS

Ad26.COV2.S continues to have a favourable benefit-risk profile when used as recommended in the currently approved indications. The Company will continue to monitor potential safety concerns in association with the use of Ad26.COV2.S. Continuous Company safety monitoring will ensure that up to date safety information is available.