JCovden : Periodic safety update report assessment

Ad-hoc PSUR after MAH surrender

This document consists of:

1. The PRAC assessment report of the ad-hoc periodic safety update report (PSUR) after MAH surrender and;
2. The PSUR itself.

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

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

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

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

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

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

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

EMA/111356/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

PRAC assessment report

Procedure no.: Ad-hoc PSUR JCOVDEN

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

Period covered by the PSUR: 25/02/2024 To: 30/09/2024

Centrally authorised Medicinal product(s):	Former Marketing Authorisation Holder
JCOVDEN (Based on the European Commission Decision issued on 26 July 2024 this product is currently withdrawn from the European market)	Janssen-Cilag International N.V.

Status of this report and steps taken for the assessment[1]

Current step	Description	Planned date	Actual Date
☐	Start of procedure	2025-01-09	2025-01-09
☐	PRAC Rapporteur's preliminary assessment report (AR)	2025-03-10	2025-03-25
☐	MS/PRAC members and MAH comments	2025-04-09	2025-04-09
☐	PRAC Rapporteur's updated assessment report following comments	2025-04-24	NA
☒	PRAC recommendation	2025-05-08	2025-05-8

Procedure resources	
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1. Background information on the procedure

On 26 July 2024, the European Commission withdrew the marketing authorisation for Jcovden (COVID-19 Vaccine Janssen (Ad26.COV2.S)) in the European Union (EU). The withdrawal was at the request of the marketing authorisation holder, Janssen-Cilag International N.V., which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons. No valid marketing authorisation is therefore available in the EU/EEA currently.

In the previous PSUSA procedure covering the period between 25/02/2023 to 24/02/2024 (EMEA/H/C/PSUSA/00010916/202402) the following was stated under section 4.

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

This assessment report reflects the assessment of the ad-hoc PSUR requested by PRAC.

2. Assessment conclusions and actions

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

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

This report covers the period from 25 February 2024 to 30 September 2024, corresponding to the expiry date of the last doses for use in non-EU countries.

During the reporting period, the MAH reported 31 March 2024 as the marketing cessation date in EU, based on commercial reasons.

During the reporting interval, 8,432,900 doses of Ad26.COV2.S were distributed and 653 doses of Ad26.COV2.S were administered worldwide. These 653 doses were administered in South Africa. No doses were administered in Europe. A total of 668,495,350 doses of Ad26.COV2.S vaccine have been distributed and 53,288,682 doses of Ad26.COV2.S vaccine have been administered worldwide from launch to 30 September 2024.

There were no signals that were undergoing evaluation at DLP of this report. There have been no Regulatory Authority requests received by the MAH to monitor a specific topic that was not considered a confirmed signal. During the reporting interval, no closed or refuted signals categorised as important potential or identified risk were identified.

Overall, assessment of the data within the current ad-hoc PSUSA does not provide significant new safety information to the known safety profile of the vaccine.

On 30 April 2024, ETF recommended updating COVID-19 vaccines to target the JN.1 variant for the 2024/2025 vaccination campaign. All marketing authorisation holders were expected to update the composition of their authorised vaccines in accordance with this recommendation. Upon enquiry by the EMA, the MAH of JCovden clarified that they did not intend to update their vaccine to any of the recommended variants of concerns (VOC), including XBB and any following. The MAH requested to withdraw the marketing authorisation in EU on 10 June 2024 for JCovden. The marketing authorisation for JCovden was withdrawn on 26 July 2024. No valid marketing authorisation is therefore available in the EU/EEA at this time.

3. Recommendations

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

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

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

Not applicable.

5. PSUR frequency

Based on the European Commission Decision issued on 26 July 2024 this product is currently withdrawn from the European market. No further PSUR submission is requested.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This report covers the period 25 February 2024 to 30 September 2024. During the reporting period, the MAH reported 31 March 2024 as the marketing cessation date in EU, based on commercial reasons.

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

The MAH requested to withdraw the marketing authorisation in EU (EU/1/20/1525/001, EU/1/20/1525/002) for JCovden (EMEA/H/C/005737) on 10 June 2024. The marketing authorisation for JCovden was withdrawn on 26 July 2024. No valid marketing authorisation is therefore available in the EU/EEA.

In the fifth Periodic Safety Update Report (PSUR) for COVID-19 vaccine Janssen (Ad26.COV2.S); covering data for the period from 25 February 2023 to 24 February 2024, the MAH was asked to short and concise present the safety data from the DLP of this PSUR (24 February 2024) up to the final use of this product (expire date end of September 2024) in an ad-hoc PSUR/procedure. This report includes the requested data.

1.2. Worldwide marketing authorisation status

The IBD for Ad26.COV2.S is 25 February 2021 based on the first authorisation in Bahrain. During the reporting period, Ad26.COV2.S is authorised in 17 countries/territories worldwide, see table 1 below.

Table 1: List of Countries/Territories Where Ad26.COV.2.S is Authorised (n=17)

Botswana	Ghana[a]	Moldova, Republic Of	Uganda
Brazil	Guinea-Bissau	Sao Tome and Principe	Vietnam[a]
Central African Republic	Lebanon	South Africa	
Comoros	Lesotho[a]	South Korea	
Georgia	Mauritius	Syrian Arab Republic	

Key: Ad26.COV2.S: Adenovirus Type 26 Coronavirus 2 Spike; n: Number of Countries

a: Licenses were active during the PBRER reporting interval, they were subsequently withdrawn (Lesotho 09 October 2024, Vietnam 02 October 2024) or expired (Ghana 01 November 2024) before finalisation of the PBRER

Rapporteur assessment comment:

The IBD of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021. In the EU Ad26.COV2.S was authorized on 11/03/2021. Ad26.COV2.S was withdrawn from the European market during the reporting interval. AD26.COV2.S is authorised in total 17 countries/territories worldwide and thus in 44 countries less compared to the last PSUR period.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

No significant actions related to safety were taken during the reporting interval covered by this report.

1.3.2. Changes to reference safety information

No significant changes were made to the CCDS (ie, CCSI) within the reporting interval.

1.3.3. Estimated exposure and use patterns

Cumulative Exposure in Clinical Trials

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

Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programmes, and 719,535 subjects to Ad26.COV2.S in the interventional clinical studies sponsored by other organisations/institutions.

Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative

A total of 668,495,350 doses of Ad26.COV2.S vaccine were distributed and 53,288,682 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 30 September 2024.

A total of 3,341,710 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 30 September 2024

Interval

A total of 8,432,900 doses of Ad26.COV2.S vaccine were distributed and 653 doses of Ad26.COV2.S vaccine were administered in worldwide from 01 March 2024 to 30 September 2024.

A total of 670 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa from 01 March 2024 to 30 September 2024.

Table 5: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting interval (01 March 2024 to 30 September 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
ROW		
Ghana	8,179,200	NR
Namibia	1,700	NR
Sierra Leone	151,200	NR
South Africa	0	653
Tanzania, United Republic of	100,800	NR
Total[d]	**8,432,900**	**653**

Key: CDC: Centers for Disease Control and Prevention, ECDC: European Centre for Disease Prevention and Control, EEA: European Economic Area, EU: European Union, NDH: National Department of Health, NR: Not Reported, ROW: Rest of World, US: United States

a Number of vaccine doses distributed were reported from EVSX Finance.

b Number of vaccine doses administered were reported from the NDH for South Africa.

c As of 09 August 2021, all entities have the ability to update or delete their previously submitted records. The use of this new functionality may result in fluctuations across metrics on the CDC COVID-19 Data Tracker as historical data are updated or deleted. The functionality will also allow for more accurate reporting and improved data quality. All reported numbers may change over time as historical data are reported to the CDC. In addition, the information within the ECDC website stated that, "All data are subject to retrospective correction" which may be a reason for decrease in the cumulative exposure in certain countries/territories. Exposure values were obtained from the most current counts as of 30 September 2024

d Number of vaccine dose distributed and administered were not reported for EEA and US region from 01 March 2024 to 30 September 2024

Rapporteur assessment comment:

During the reporting interval, 8,432,900 doses of Ad26.COV2.S were distributed and 653 doses of Ad26.COV2.S were administered worldwide. These 653 doses were administered in South Africa. No

doses were administered in Europe.

A total of 668,495,350 doses of Ad26.COV2.S vaccine have been distributed and 53,288,682 doses of Ad26.COV2.S vaccine have been administered worldwide from launch to 30 September 2024.

1.3.4. Data in summary tabulations

During the reporting interval, 1,530 serious ARs and 907 nonserious ARs were received from spontaneous sources, and 31 serious ARs were received from non-interventional post-marketing studies and other solicited sources. For the reporting interval of 25February 2024 to 30 September 2024, the AR count is notably less than the number of the ARs identified from the previous PBRER reporting interval of 25February 2023 to 24 February 2024 (4,970 serious Ars and 6,620 nonserious ARs). This decrease in number may be due to the lower exposure to the vaccine compared to last reporting interval.

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 (957)
- Nervous System Disorders (367)
- Musculoskeletal and Connective Tissue Disorders (174)
- Gastrointestinal Disorders (102)
- Cardiac Disorder (100)

Cumulatively, 103,269 serious ARs (101,967 spontaneous, 1,302 from non-interventional post-marketing studies and other solicited sources) were received by the Marketing Authorisation Holder (MAH).

Rapporteur assessment comment:

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

No new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Completed Clinical Trials

A "completed clinical trial" is defined as a trial for which a final clinical study report is available at the time of the data-lock for this PBRER reporting interval.

During the reporting interval, 3 Company-sponsored interventional clinical trials (VAC31518COV2004, VAC31518COV3003, and VAC18193RSV2008) of Ad26.COV2.S were completed.

Trial VAC31518COV2004

This was a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant (second and/or third trimester of pregnancy) subjects aged ≥18 to ≤45 years. In this trial, Ad26.COV2.S was assessed as a single dose in pregnant

women who were previously vaccinated with another COVID-19 vaccine regimen or who were vaccine naive at study entry. All randomised subjects were analysed by vaccination group, based on prior to baseline vaccinations with COVID-19 vaccines:

- mRNA group: subjects with a previous primary vaccination (2 doses) or homologous booster vaccination with COVID-19 Vaccine, mRNA (BNT162b2) (Pfizer-BioNTech) or COVID-19 Vaccine, mRNA (mRNA-1273) (Moderna).
- Other group: subjects with previous COVID-19 vaccination (excluding mRNA group), irrespective of previous schedule and vaccine (includes heterologous regimens).
- Vaccine-naive group: subjects who had not received a prior COVID-19 vaccination. A booster vaccination with a single dose of Ad26.COV2.S at 5×10^{10} vp was offered. The booster vaccination was administered not earlier than 2 months after administration of the subject's initial Ad26.COV2.S vaccination in the trial.

Of the 67 subjects screened in this trial, a total of 51 subjects received at least 1 dose of the study vaccine (Ad26.COV2.S): 12, 10, and 29 in the mRNA, Other, and Vaccine-naive groups, respectively. In the Vaccine-naive group, 13 subjects also received an Ad26.COV2.S booster vaccination. A summary of safety data is presented below:

Safety Summary

Death, Serious Adverse Events, Discontinuations Due to Adverse Events and, Adverse Event of Special Interest, and Medically-Attended Adverse Events

There were no AEs with fatal outcome in adult subjects. After a single administration of Ad26.COV2.S, SAEs were reported in 4 (33.3%), 2 (20.0%), and 3 (10.3%) subjects in the mRNA, Other, and Vaccine-naive groups, respectively.

Across vaccination groups, gestational hypertension was reported in 2 (3.9%) subjects; other SAEs by PT occurred in at most 1 (2.0%) subject. One subject in the Other group experienced a Grade 4 SAE of placental insufficiency at 36 days after vaccination during the third trimester of pregnancy, which was considered related to the study vaccine by the investigator and resolved. This event was followed by a Grade 4 SAE of premature baby, which was considered not related to the study vaccine.

No SAEs were reported after the optional booster dose (ie, booster vaccination period) in vaccine naive subjects. No subjects discontinued the trial due to an AE.

A suspected AESI of thrombocytopenia was reported in 2 subjects in the Vaccine-naive group and was considered not to be related to the study vaccine by the investigator for both subjects. None of the subjects had thrombosis and thrombocytopenia reported concomitantly; therefore, there were no suspected AESIs that qualified for TTS assessment, and no cases of TTS were reported in this trial.

After a single administration of Ad26.COV2.S, Medically-Attended Adverse Events (MAAEs) were reported in 6 (50.0%), 2 (20.0%), and 7 (24.1%) subjects in the mRNA, Other, and Vaccine-naive groups, respectively. None of these events were considered related to the study vaccine by the investigator. In 1 (10.0%) subject in the Other group, a MAAE of pre-eclampsia occurred within 28 days after vaccination (ie, Post-dose 1). No MAAEs were reported after the optional booster dose (ie, booster vaccination period) in the Vaccine-naive group. None of the MAAEs led to study discontinuation.

Pregnancy outcomes and pregnancy-related AEs

In subjects with pregnancy outcome, a total of 43/47 (91.5%) subjects had a live term birth, and 4/47(8.5%) a live preterm birth. There were neither stillbirths, nor abortions. Delivery complications were reported in 7/47 (14.9%) adult subjects. Pregnancy-related AEs were reported in 4 (50.0%), 2 (40.0%),

and 3 (21.4%) subjects after a single administration ofAd26.COV2.S during the second trimester of pregnancy, and in 1 (25.0%), 3 (60.0%), and 1 (6.7%) subjects after a single administration of Ad26.COV2.S during the third trimester of pregnancy, in the mRNA, Other, and Vaccine-naive groups, respectively.

Neonates/infants

Deaths, Serious Adverse Events, Adverse Events Leading to Study Discontinuation, Adverse Event of Special Interest, and Medically-Attended Adverse Events

Serious adverse events in neonates/infants were followed up from birth until 12 months postpartum. One (10.0%) neonate/infant from a mother in the mRNA group had an AE of ventricular septal defect (VSD) with a fatal outcome. Upon physical examination, this neonate was diagnosed with VSD 1 day after the neonate's birth and died on Day 106 due to congenital VSD. This event of VSD was not considered related to the mother's study vaccine exposure.

Serious adverse events were reported in 2 (20.0%), 2 (25.0%), and 3 (10.3%) neonates/infants from mothers in the mRNA, Other, and Vaccine-naive groups, respectively, during the Postnatal Follow-up 1 period. Similar or lower SAE incidences were reported during Postnatal Follow-up periods 2 and 3. Each SAE by PT occurred in at most 1 (2.1%) neonate/infant, except bronchiolitis, which occurred in 2 (4.3%) neonates/infants during the Postnatal Follow-up 2 period. None of the SAEs were considered related to the mother's study vaccine by the investigator.

No neonates/infants discontinued the trial due to an AE.

Multisystem Inflammatory Syndrome in Children in neonates/infants was to be considered an AESI in this trial. No cases of multisystem inflammatory syndrome were reported in neonates/infants.

Medically-attended adverse events were reported in 4 (40.0%), 2 (25.0%), and 2 (6.9%) neonates/infants from mothers in the mRNA, Other, and Vaccine-naive groups, respectively, during the Postnatal Follow-up 1 period, and in 3 (30.0%), 2 (25.0%), and 4 (13.8%) neonates/infants, respectively, during the Postnatal Follow-up 2 period. The most frequently reported MAAEs by PT were bronchiolitis (0 and 4 [8.5%] neonates/infants during the Postnatal Follow-up 1 and 2 periods, respectively), influenza (1 [2.1%] and 2 [4.3%] neonates/infants, respectively), and jaundice neonatal (2 [4.3%] and 0 neonates/infants, respectively). Other MAAEs occurred in at most 1 neonate/infant during the Postnatal Follow-up 1 and 2 periods. None of the MAAEs led to study discontinuation.

Birth Outcomes

In neonates where birth outcome was assessed, 41/46 (89.1%) had a normal birth outcome. Other birth outcomes were low birth weight (mother in the mRNA group), complications (3 cycles of positive pressure ventilation needed after apnoea in one term neonate, and transient tachypnoea of the newborn in one preterm neonate, both from mothers in the Vaccine-naive group), and 2 preterm neonates without complications (both from mothers in the Vaccine-naive group). For 1 preterm neonate, the birth outcome was not reported in the electronic case report form, but a pregnancy outcome and Grade 4 SAE of premature baby was reported for the neonate's mother. Therefore, this preterm neonate was not included in the birth outcome analysis of the neonates, while it was included in the AE safety analysis of the adults. Note that the neonate who died following an AE of VSD had a normal birth outcome, as this event started 1 day after the neonate's birth. Overall, the safety and reactogenicity profile of Ad26.COV2.S is considered acceptable in pregnant women after a single dose in women who were vaccine naive or previously received a COVID-19 vaccine, and after 2 doses when administered to vaccine-naive women. No unexpected safety concerns were identified.

Trial VAC31518COV3003

This was 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. The primary purpose of this study was to aid in the establishment of end-expiry specifications for the Ad26.COV2.S regimens that were assessed in the Phase 3 efficacy studies. This trial consisted 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 were evaluated. In the sub-trial, additional adult subjects aged 18 to 55 years were enrolled to further characterise the innate, pro-inflammatory, and other relevant (eg, pro thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events.

Of the 4,801 subjects screened in this trial, a total of 1,593 subjects received at least 1 dose of the study vaccine (Ad26.COV2.S) in main and sub study. A summary of safety data is presented below:

Safety Summary

Deaths, Serious Adverse Events, Discontinuation Due to Adverse Events, Adverse Event of Special Interest, and Medically-Attended Adverse Events

Grade 4 SAEs with fatal outcome were reported for 2 subjects:

Drowning was reported for 1 subject in the 9×10^{10} vp group during the first follow-up period (99 days after receiving study vaccination on Day 1; the subject only received one dose of study vaccine). Death for undetermined reason was reported for 1 subject in the 1.25×10^{10} vp group during the third follow-up period (313 days after receiving the second study vaccination on Day57). Both SAEs were considered by the investigator as not related to the study vaccine. During the entire trial, SAEs were reported in 2.0% (32/1,593) subjects. The incidence of SAEs was numerically higher in the highest dose (9×10^{10} vp) group (4.5% [13/288]), and similar across the other dose groups (≤1.8%). The majority of SAEs were reported during the follow-up periods. By PT none of the SAEs were reported in more than 1 subject, except for abortion spontaneous, which occurred in 1 subject each in the 5×10^{10} vp and the 9×10^{10} vp groups. Three Grade 4 SAEs were reported: suicide attempt in 1 subject in the 2.5×1010 vp group, death (for undetermined reason) in 1 subject in the 1.25×10^{10} vp group, and drowning in 1 subject in the 9×1010 vp group. Most other SAEs were Grade 3 in severity. None of the SAEs were considered related to study vaccine by the investigator.

AEs leading to vaccination regimen discontinuation (mainly COVID-19) were reported in 13 subjects: in 0.4% (6/1,593) subjects post-dose 1 and 0.5% (8/1,579) subjects during follow up 1. The overall incidence of AEs leading to vaccination regimen discontinuation was similar in all dose groups. None of the AEs leading to vaccination regimen discontinuation were Grade 3 or 4 in severity and none were serious. AEs leading to vaccination regimen discontinuation that were considered related to study vaccine by the investigator were reported in 4 subjects: COVID-19 in 1 participant each in the 1.25×10^{10} vp, 2.5×10^{10} vp, and 3.5×10^{10} vp groups and vaccination site erythema in 1 participant in the7×10^{10} vp group.

None of the subjects had thrombosis and thrombocytopenia reported concomitantly; therefore, there were no suspected AESIs that qualified for TTS assessment, and no cases of TTS were reported in this trial.

During the entire trial, MAAEs were reported in 16.1% (256/1,593) subjects. MAAEs were reported in a similar proportion of subjects in all dose groups (ranging from 12.3% [35/285] to 18.8% [54/288]). By PT, the most frequently reported MAAEs were influenza and COVID-19 (each reported in 2.6% [42/1,593] of all subjects).

Overall, the safety and reactogenicity profile of the Ad26.COV2.S vaccine administered as a 2-dose schedule (with the second vaccination 56 days after the first vaccination) in healthy adults was

considered acceptable at all doses levels studied (9×10^{10} vp, 7×10^{10} vp, 5×10^{10} vp, 3.5×10^{10} vp, 2.5×10^{10} vp, and 1.25×10^{10} vp). No new safety signals were identified in this trial.

Trial VAC18193RSV2008

This was a Phase 1, randomised, observer-blind, multicentre trial to evaluate innate and pro-inflammatory responses of an Ad26.RSV.preF-based vaccine, Ad26.COV2.S and Ad26.ZEBOV vaccines in adult subjects aged 18 to 59 years in stable health. Of the 215 subjects screened in this trial, a total of 160 subjects received at least 1 dose of the study vaccine (Ad26.COV2.S, or Ad26/protein preF RSV, or Ad26.ZEBOV) in the trial. A summary of safety data is presented below:

Safety Summary

Deaths, Serious Adverse Events, Discontinuation Due to Adverse Events, Adverse Event of Special Interest, and Medically-Attended Adverse Events

There were no deaths during the trial. Two subjects in the Ad26.ZEBOV group had a total of3 SAEs in the post-dose 1 period. None of the events were considered to be related to study vaccine by the investigator. One participant had depression, and 1 participant had 2 SAEs (end stage renal disease and renal transplant). The latter participant had end stage renal disease at screening/Day 1 which was discovered after randomisation and vaccination in the trial; this pre-existing condition was identified as a major protocol deviation. The participant subsequently had a renal transplant during the trial. Two subjects, 1 in each of the Ad26.COV2.S and Ad26/protein preF RSV groups had SAEs (ligament injury and umbilical hernia, respectively) during the open label follow-up period.

No subjects discontinued from the trial due to AEs. One subject in the Ad26.ZEBOV group had an unsolicited AE (end stage renal disease; also reported as an SAE) leading to discontinuation of the Day57 MVA-BN-Filo vaccination but completed the trial. Three subjects had events (thrombocytopenia/platelet count decreased) which were suspected AESIs; none of the suspected AESIs qualified for assessment by the TTS Adjudication Committee. None of the subjects reported venous thromboembolism or arterial thrombotic events.

- One subject in the Ad26.COV2.S group had 2 suspected AESIs, pseudothrombocytopenia and worsening thrombocytopenia. Pseudothrombocytopenia of Grade 2 severity started on Day 29 and resolved 44 days later; it was not serious and was not considered to be related to study vaccine. Worsening thrombocytopenia of Grade 3 severity started on Day 44 and resolved 29 days later; it was not serious and was considered to be related to study vaccine. Due to an error in the conversion of laboratory units, the platelet counts on Days 44, 47, 54, 57, 59, 61, and 64 were reported to be of Grade 4 severity instead of Grades 1 to 3. The platelet count was reported as within normal range on the next databased assessment (Day 113). There were no clinical signs of thrombosis. The case was diagnosed as pseudothrombocytopenia related to the use of an ethylenediaminetetraacetic acid tube. The case did not fulfil the definition of a TTS and therefore was not adjudicated by the TTS team.
- One subject in the Ad26.COV2.S group had 1 suspected AESI, platelet count decrease (single observation), on Day 29. The event was of Grade 1 severity, resolved 31 days later, was not serious, and was considered to be not related to study vaccine.
- One subject in the Ad26/protein preF RSV group had 1 suspected AESI, thrombocytopenia, on Day 30. The event was of Grade 1 severity, resolved 15 days later, was not serious, and was considered to be related to study vaccine.

No subjects reported AESI during the trial, ie, events that were identified as AESI and assessed following a request from regulatory authorities in previous studies with the Ad26/protein preF RSV vaccine.

1.3.5.2. Ongoing Clinical Trials

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

During the reporting interval, no Company-sponsored interventional clinical trial ofAd26.COV2.S was ongoing.

Independent Data Monitoring Committee/Data Safety Monitoring Board

During the reporting interval, no clinical trials were ongoing, hence, Independent Data Monitoring Committee/ Data Safety Monitoring Board is not applicable for this PBRER.

Long-term Follow-up

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

Other Therapeutic Use of Medicinal Product

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

New Safety Data Related to Fixed Combination Therapies

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

Rapporteur assessment comment:

During the reporting interval, three MAH sponsored clinical trials of Ad26.COV2.S were completed (VAC31518COV2004, VAC31518COV3003, and VAC18193RSV2008). No clinical trials were ongoing.

No new safety concerns were generated in these trials.

1.3.5.3. Findings From Non-Interventional Studies

Real World Evidence Summary for Ad26.COV2.S

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

1.3.5.4. Other Clinical Trials and Sources

Completed Clinical Study

During the PBRER reporting interval, the following 4 interventional clinical studies were completed forAd26.COV2.S: 1 interventional clinical study (VAC31518COV2012) sponsored by Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand); 1 interventional clinical study (VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by SAMRC; 1 interventional clinical study (VAC31518COV4012) sponsored by National and Kapodistrian University of Athens; University Research Institute of Maternal and Child Health & Precision Medicine; and 1 interventional clinical study (DMID 21-0012) sponsored by NIH.

<u>Trial VAC31518COV2012</u>

This was a Phase 1/2, prospective, multicentre, observer-blind adaptive trial to assess the safety, reactogenicity, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 years of age in Study Part A and Part B. A total of 570 subjects were recruited. Enrolment of groups were open-label allocation and assessor-masked.

Safety Summary

During the entire study period, Grade 1–3 SAEs occurred in 64 (13.8%) of 465 subjects in the safety analysis population: 52 (14.4%) subjects in Arm A1 and 12 (11.5%) in Arm A2). No SAEs were medically assessed as related to the study booster. No SAEs were fatal or resulted in persistent disability or incapacity. The SAEs in 60 subjects resolved completely; in the remaining 4 (0.9%) subjects, the SAEs (pemphigus vulgaris, prostate cancer, herniated lumbar disc and liver cancer) were ongoing at the study cut-off. In 48 (10.3%) subjects, the SAEs were confirmed SARS-CoV-2 infections, for which 6 (1.3%) subjects required hospitalisation; all 48 affected subjects recovered fully. All SARS-CoV-2 infections were mild or moderate except in 1 subject (0.2%), whose infection was classified as severe because they were treated with favipiravir. The individual was treated as an outpatient and recovered after 10 days. Adverse events of special interests occurred in 3 (0.6%) subjects in Arm 1 and all were medically assessed as not related to the study booster. Grade 2 ageusia in the context ofSARS-CoV-2 infection occurred in 2 subjects, and resolved within 9 and 10 days, respectively. Grade 3 pemphigus vulgaris occurred in 1 subject 2.5months after the booster, required hospitalisation and improved. The subject's condition remained stable at the study cut-off. Seven pregnancies occurred during the study, which resulted in 6 normal deliveries at term. These pregnancies were confirmed 2.5 weeks to 9 months after the booster injection. One pregnancy that was confirmed almost 8 months after the booster injection resulted in spontaneous abortion after in vitro fertilisation. Five newborns were healthy; 1 had a minor congenital anomaly (micro-cleft lip, requiring no surgical intervention) that was medically assessed as unrelated to the study booster given to a subject in her first trimester of pregnancy.

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

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

Safety Summary

The Sisonke 2 study provided a homologous boost at least 6 months after administration of the priming dose of Ad26.COV2.S for healthcare workers enrolled on the Sisonke Phase 3b implementation study. A total of 2,350 AEs were reported by 2,117 of the 240,888 (0.88%) subjects enrolled; 1,625 of the 2,350 reported events were reactogenicity events and 28 adverse events which met seriousness criteria. No cases of thrombosis and thrombocytopaenia syndrome were reported; all AEs including thromboembolic disorders occurred at a rate below the expected population rates apart from the 1 reported case of Guillain-Barre syndrome.

During the study, 2 non-COVID-19 related deaths occurred that were deemed not related to vaccination. Thirteen deaths occurred from breakthrough COVID-19 infections that were deemed unrelated.

Trial VAC31518COV4012

This was a study in subjects >18 years of age to investigate the association of total antibodies, neutralising antibodies, and T-cell responses against SARS-CoV-2 spike protein with epidemiological and clinical parameters in a cohort of vaccinees after initial immunisation with Ad26.COV2.S and boosting with either Ad26.COV2.S or mRNA vaccines. In addition, it investigated the initial antibody response 1 month

after immunisation and then followed the antibody kinetics during a 1-year period and the T-cell responses with sequencing to the T-cell repertoire after initial immunisation with Ad26.COV2.S and boosting with either Ad26.COV2.S or mRNA vaccines.

Safety Summary

After the booster dose, the most common local AE for both vaccines was pain (60%, 6/10), while the most common systemic AEs were myalgias (40%, 4/10) after the Ad26.COV2.S vaccine and fatigue (50%, 5/10) after the BNT162b2 vaccine. No SAE was recorded.

Trial DMID 21-0012

This was a Phase 1/2, open-label study in individuals, 18 years of age and older, who were in good health, had no known history of COVID-19 or SARS-CoV-2 infection, and met all other eligibility criteria. This trial was 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 (mRNA1273 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/ Johnson & Johnson).

Safety Summary

There were no deaths and no SAEs related to study product reported. Additionally, there were no AESIs or NOCMCs reported as related to study product and only one MAAE (Group 5E-vomiting) recorded as related to study product. Local, solicited and unsolicited AEs were largely similar to those reported for the primary EUA vaccine series with 72% of subjects reporting at least 1 local solicited AE and 82% reporting at least 1 systemic solicited AE. The events reported were predictable, with pain predominating as the most common local symptom, and fatigue ranking as the most common solicited systemic event. Chills, headache, and myalgia were reported as frequent solicited systemic symptoms, but most were mild-moderate in nature and resolved by Day 2 following vaccination. Unsolicited AEs related to study product were not common; 19 subjects reported related AEs, the most common of which were dizziness (n=3) and insomnia (n=3).

Between study groups, a slight trend was noted in terms of increased solicited systemic AEs in the mRNA-primed subjects with 78% of Group 5E and 74% of Group 6E reporting at least 1 event compared to 62% of Group 4E subjects. The reverse finding was noted with local solicited AEs, with 61% of Group 5E and 69% of Group 6E reporting at least 1 event compared to 76% of Group 4E subjects. However, the numbers were low and not statistically significant. Throughout the duration of the study, a number of AESIs were reported in other populations as related to EUA SARS-CoV-2 vaccines, including vaccine-induced immune thrombocytopenia and thrombosis with adenoviral-vectored vaccines and myocarditis with mRNA vaccines. All of these reportable findings were included as AESIs in subsequent protocol amendments owing to the adaptive nature of the trial, but no findings were noted in study subjects. Additionally, the single pregnancy that occurred in a trial subject was treated with a therapeutic abortion.

Ongoing Clinical Study

During the PBRER reporting interval, 3 interventional clinical studies sponsored by other organisations/institutions were ongoing for Ad26.COV2.S: 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by University Hospital Southampton National Health Service Foundation Trust; 1 interventional clinical study (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute Not for Profit Company; and 1 interventional clinical study (VAC31518COV3018) sponsored by Mayo Clinic.

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

Study COV-BOOST (VAC31518COV2009)

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

At the time of DLP of this PBRER, 2,883 subjects were enrolled, of which 214 received Ad26.COV2.S. During the reporting interval, no relevant safety information related to Ad26.COV2.S from this clinical study became available.

Trial VAC31518COV2016 (AUR1-8-341)

This is a Phase 2a, randomised, observer-blind, multicentre study of the safety and immunogenicity ofCOVID-19 vaccine strategies in HIV-infected and HIV-uninfected adults. A total of 750 evaluable HIV-infected (660) and HIV-uninfected (90) adult subjects meeting all entry criteria (all inclusion and no exclusion criteria) were planned to be enrolled in 3 treatment strategies in 3 subject groups dependent on prior vaccination with a single dose of Janssen (Group 1), 2 doses of Pfizer (Group 2), or no prior COVID-19 vaccination with evidence of prior SARS-CoV-2 infection (Group 3).

At the time of DLP of this PBRER, 231 subjects received Ad26.COV2.S in this study.

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

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

Trial VAC31518COV3018

This is a Phase 3, prospective, open-label clinical trial with 1 randomised arm to evaluate the response of a heterologous additional dose with the Ad26.COV2.S to provide vaccine induced immunity for immunocompromised kidney transplant patients after receiving 2 or more doses of the Pfizer or Moderna COVID-19 vaccine.

At the time of DLP of this PBRER, 55 subjects received Ad26.COV2.S in this study.

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

Rapporteur assessment comment:

During the reporting interval, 4 interventional clinical studies sponsored by other organisations/institutions were completed forAd26.COV2.S: VAC31518COV2012, VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}], VAC31518COV4012 and DMID 21-0012

During the reporting interval, 3 interventional clinical studies sponsored by other organisations/institutions were ongoing for Ad26.COV2.S: COV-BOOST [VAC31518COV2009]) , VAC31518COV2016 [AUR1-8-341] and VAC31518COV3018.

No new safety concerns were identified in these studies.

Medication Errors

Primary dose case

During this reporting interval, a total of 2 medically unconfirmed, initial, primary dose cases reporting medication errors were retrieved. None of these cases concerned paediatric patients. These 2 cases

reported 3 nonserious medication error EOI. Both primary dose cases received during the reporting interval were reported from the US and concerned the product storage, administration or quality.

Cumulatively, 2,559 (1,835medically confirmed and 724 medically unconfirmed), primary dose cases reporting medication errors were retrieved. Of these 2,559 cases, 377 concerned paediatric patients. The remaining 2,182 cases reported a total of 2,923 EOI (48 serious; 2,875 nonserious).

During this reporting interval, no initial primary dose cases reporting medication errors in the paediatric population were retrieved.

Booster dose case

During this reporting interval, a total of 5 (2 medically confirmed and 3 medically unconfirmed), initial cases reported as booster dose were identified. Of these 5 cases, none concerned paediatric patients. Of these 5cases, there were 4 serious and 1 nonserious case, which reported a total of 5 nonserious medication error EOI. Of these 5cases reported as booster dose received during the reporting interval, the most frequently reported countries/territories of origin were Germany (n=4), followed by the Spain (n=1). All concerned interchange of vaccine products contained additional AEs (classified as medication errors with harm).

Cumulatively, 1,104 (296 medically confirmed and 808 medically unconfirmed) cases reported as booster dose were identified. Of these 1,104 cases, 7 concerned paediatric patients. The remaining 1,097 booster cases reported a total of 1,135mediation error EOI (32 serious; 1,103 nonserious) a.

During this reporting interval, no initial booster cases reporting medication errors in the paediatric population were retrieved.

Rapporteur assessment comment:

During the reported period, few cases (n=2 primary dose; n=5 booster dose) reported medication errors.

No new safety concern arises here.

Non-Clinical Data

During the reporting interval, no non-clinical studies were conducted for Ad26.COV2.S.

Literature

Product-Specific Literature

Kim HJ, Kim MH, Park SJ, Choi MG, Chun EM. Autoimmune adverse event following COVID-19 vaccination in Seoul, South Korea*. J Allergy Clin Immunol*. 2024;153(6):1711-1720.

Background: There is growing evidence that the coronavirus disease 2019 (COVID-19) vaccination can affect the regulation of the immune system, leading to the development of autoimmune diseases. However, the autoimmune adverse events (AEs) after COVID-19 vaccination remain largely unclear.

Objective: We sought to investigate the autoimmune AEs after COVID-19 vaccination from a population-based cohort in South Korea.

Methods: A total of 4,203,887 participants, representing 50% of the population residing in Seoul, were recruited from the National Health Insurance Service database and then divided into 2 groups on the

basis of COVID-19 vaccination. The cumulative incidence, hazard ratios (HRs), and 95% CIs of autoimmune AEs were assessed following COVID-19 vaccination.

Results: The incidence of vitiligo has been observed to be significantly higher in the vaccination group compared with the no vaccination group. The cumulative incidence of vitiligo began to show a significant difference starting 2 weeks after vaccination, and it reached 2.2% in the vaccination group and 0.6% in the no vaccination group by 3 months after COVID-19 vaccination. Vitiligo (HR, 2.714; 95% CI, 1.777-4.146) was an increased risk among autoimmune AEs. Furthermore, the risk of vitiligo was the highest for heterologous vaccination (HR, 3.890; 95% CI, 2.303-6.573) compared with using cDNA vaccine (HR, 2.861; 95% CI, 1.838-4.453) or mRNA vaccine (HR, 2.475; 95% CI, 1.607-3.813).

Conclusions: Vitiligo as an autoimmune AE was noted to be substantially higher in the COVID-19-vaccinated group compared with the controls. Therefore, the occurrence of vitiligo could be considered as one of the significant AEs post-COVID-19 vaccination.

MAH Commentary on Citation: *The authors conducted a large population-based cohort study in a specific region and does not encompass the entire population of South Korea. Of the 2,086,709 subjects remaining in the vaccination group after all exclusion criteria were applied by the authors, a total of 12 subjects received Ad26.COV2.S as a first dose and 9 subjects as a second dose as part amheterologous dosing regimen. No subjects were exclusively administered Ad26.COV2.S. No conclusions regarding Ad26.COV2.S were presented by the authors. Based on the paucity of data for Ad26.COV2.S within a heterologous vaccination regimen, no new safety information regarding vitiligo is detected at this time.*

Class Effect Literature

Couvillion S,Nakayasu ES,Webb-Robertson B-JM, et al. Associations between SARS-CoV-2 Infection or COVID-19 Vaccination and Human Milk Composition: A Multi-Omics Approach. *bioRxiv.*2024.

The risk of contracting SARS-CoV-2 via human milk-feeding is virtually non-existent. Adverse effects of COVID-19 vaccination for lactating individuals are not different from the general population, and no evidence has been found that their infants exhibit adverse effects. Yet, there remains substantial hesitation among this population globally regarding the safety of these vaccines. Herein we aimed to determine if compositional changes in milk occur following infection or vaccination, including any evidence of vaccine components. Using an extensive multi-omics approach, we found that compared to unvaccinated individuals SARS-CoV-2 infection was associated with significant compositional differences in 67 proteins, 385 lipids, and 13 metabolites. In contrast, COVID-19 vaccination was not associated with any changes in lipids or metabolites, although it was associated with changes in 13 or fewer proteins. Compositional changes in milk differed by vaccine. Changes following vaccination were greatest after 1-6 hours for the mRNA-based Moderna vaccine (8 changed proteins), 3 days for the mRNA-based Pfizer (4 changed proteins), and adenovirus-based Johnson and Johnson (13 changed proteins) vaccines. Proteins that changed after both natural infection and Johnson and Johnson vaccine were associated mainly with systemic inflammatory responses. In addition, no vaccine components were detected in any milk sample. Together, our data provide evidence of only minimal changes in milk composition due to COVID-19 vaccination, with much greater changes after natural SARS-CoV-2 infection.

IMPORTANCE The impact of the observed changes in global milk composition on infant health remain unknown. These findings emphasize the importance of vaccinating the lactating population against COVID-19, as compositional changes in milk were found to be far less evident after vaccination compared to SARS-CoV-2 infection. Importantly, vaccine components were not detected in milk after vaccination.

MAH Commentary on Citation: *Use in breastfeeding women is identified as missing information in the product's Core Risk Management Plan (cRMP) (version 8.0, 06 February 2024). Moreover, nothing is*

reported about any association of the breast milk composition and Covid-19 vaccination in the product's RSIs. The current study found that "[…] compared to the mRNA vaccines, the J&J vaccine elicited the most change in milk composition (13changed proteins at 3 days). […] Proteins that changed after both natural infection and the Company vaccine were associated mainly with systemic inflammatory responses." However, "[…] impact on infant health of these changes remains unknown." Nevertheless, the authors stated that "These findings emphasise the importance of vaccinating the lactating population against COVID-19, as compositional changes in milk were found to be far less evident after vaccination compared to SARS-CoV-2 infection." No safety observation is identified at this time.

Wang JJ, Schonborn L, Warkentin TE, et. al. Antibody Fingerprints Linking Adenoviral

Anti-PF4 Disorders*. N Engl J Med*. 2024;390(19):1827-1829. No abstract available.

MAH Commentary on Citation: *Anti-PF4 antibodies were obtained from 4 patients with "VITTlike clinical and laboratory features" after wild-type adenoviral infection. These patients had no history of exposure to adenoviral-based vaccines or heparin (for detailed data see Table S1 of the Supplementary Appendix, (Jing 2024)and the cited references. (Warkentin 2023; Campello 2023;Schönborn 2023)*

The authors performed proteomic analysis on these samples and compared the results with the consensus anti-PF4 antibody fingerprints from patients with classic VITT. They found highly similar amino acid fingerprints in the antigen-binding sites, leading to superimposable molecular structures between the VITT-like anti-PF4 antibodies and those identified in patients with VITT. The authors concluded that adenovirus, rather than other vaccine constituents, directly or indirectly induces the formation of platelet-activating anti-PF4 antibodies. It is noted, however, that the specific wild-type adenovirus serotype is not reported, and the authors acknowledged that no antigen inducing the formation of platelet-activating anti-PF4 antibodies has been identified. Additionally, the current work does not include analysis of control (without wild type adenoviral infection) samples, therefore no new safety information identified at this time.

Rapporteur assessment comment:
No new safety concerns were identified here.

1.3.6. Lack of efficacy in controlled clinical trials

Although protection with a single dose of Ad26.COV2.S in adults ≥18 years of age, including in adults ≥60 years of age against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries, regions, and emerging SARS-CoV-2 variants, including VOC/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 end-of-study analysis of the Phase 3 trial VAC31518COV3009, in which an Ad26.COV2.S booster dose was administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increased after a homologous booster dose administered 2 months after the single-dose primary vaccination.

When considering the VE against SARS-CoV-2 variants, including VOCs/VOIs, observed in Trial VAC31518COV3001, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or CIs were wide. Differences were observed in protection against moderate to severe/critical

COVID-19. No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI]: 58.9% [43.40; 70.50] at least 28 days after vaccination) for the Alpha VOC and other variants was observed, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<37%). The VE estimate (95% CI)

for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). For severe/critical COVID-19, the VE estimates were 61% to 91% across variants with sufficient COVID-19 cases, such as Beta, Gamma VOCs, and Lambda, Mu VOIs. In summary, in the double-blind randomised placebo-controlled trial, a single dose of Ad26.COV2.S provided at least 6 months of protection against severe/critical disease, hospitalisation, and death, with varying degrees of protection against symptomatic disease depending on the variant. Since the clinical trial VE estimates are below 100%, particularly for mild and moderate disease, breakthrough cases in vaccinated individuals are expected to occur.

Rapporteur assessment comment:

As concluded in previous PSUR, reduced vaccine effectiveness has been observed for variants (i.e. Delta, Gamma, Mu and Lambda) compared to Alpha strain. No data regarding effectiveness against omicron variants has been presented.

1.3.7. Late-breaking information

Since the DLPP of 30 September 2024, no late-breaking information has been identified regarding Ad26.COV2.S.

2. Signal and risk evaluation

2.1. Summary of safety concerns

At the Beginning of the Reporting Interval

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting interval to be included in the Ad26.COV2.S PBRER is based on the cRMP (version 8.0, dated 06 February 2024) and is summarised in Table 44.

In addition, the summary of safety concerns is also based on the following:

- Important risk and missing information definitions provided in the ICH E2C guidelines on the PBRER and GVP Module VII - Periodic Safety Update Report
- Any additional safety concerns per other regional or country/territory-specific RMP requirements, as applicable.
- European Union (EU) RMP: version 7.1 (dated 13 June 2023).
- European Medicines Agency (EMA) core PSUR 19 guidance (EMA/362988/2021 dated 08 July 2021).

Table 44: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Interval

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

Key: EU: European Union; RMP: Risk Management Plan; VAERD: Vaccine-associated enhanced respiratory disease

a. This topic is included in the EU RMP only.

At the End of the Reporting Interval

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

The EU RMP version 7.1 (dated 13 June 2023) was updated to version 8.2 (dated 12 July 2024) with the removal of the missing information "Interaction with other vaccines. The EU RMP version 8.2 (dated 12 July 2024) was further updated to version 8.315 (dated 04 June 2024) and submitted on 28 June 2024 under Type II variation Procedure No. EMEA/H/C/005737/II/0078/G to EMA, however before the completion of the procedure the marketing authorisation was withdrawn.

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

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

Key: EU: European Union; RMP: Risk Management Plan; VAERD: Vaccine-associated enhanced respiratory disease

Rapporteur assessment comment:

During the reporting interval, the missing information "interaction with other vaccines" was removed.

2.2. Signal evaluation

2.2.1. Ongoing or closed signals

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

There have been no Regulatory Authority requests received by the Company to monitor a specific topic that was not considered a confirmed signal.

During the reporting interval, no closed or refuted signals categorised as important potential or identified risk were identified.

2.3. Evaluation of risks and safety topics under monitoring

New Information on Important Identified Risks

Thrombosis With Thrombocytopenia Syndrome

Results/Discussion

Primary Dose

During this reporting interval, a total of 8 medically confirmed initial, primary dose cases reporting TTS were retrieved. These serious cases reported a total of 8 serious EOI. Cumulatively, 387 (311 medically confirmed and 76 medically unconfirmed) primary dose cases reporting TTS were retrieved. There were 385serious and 2 nonserious cases which reported a total of 1,292 EOI (1267 serious, 25nonserious). A single case may report more than 1 EOI. Of these 8 initial, primary dose cases received, the most frequently reported countries/territories of origin were Netherlands (n=3) and the US (n=2). These cases concerned 2 males, 2 females, and 4 cases did not report sex. The age range was from 29 to 78 years.

The EOI reported in all these 8 cases received in the reporting interval was Thrombosis with thrombocytopenia syndrome (n=8). The Time to Onset (TTO) was not reported in all the 8 cases. Where reported (n=1), outcome was reported as resolved. Of these 387 primary dose cases received cumulatively, the Company identified 344 primary dose cases that met case definition for TTS and are stratified by age group and sex and for Brighton Collaboration (BC), Centers for Disease Control (CDC), and Pharmacovigilance Risk Assessment Committee (PRAC) criteria.

Booster Dose

During this reporting interval, 1 medically confirmed initial, booster dose serious case reporting TTS was retrieved and reported 1 serious EOI. This case was heterologous and reported from Italy. The EOI reported during the reporting interval was Thrombosis with thrombocytopenia syndrome (n=1). The TTO and the outcome was not reported.

Cumulatively, 10 (9 medically confirmed and 1 medically unconfirmed) booster dose cases reporting TTS were retrieved. These 10 serious cases reported a total of 32 serious EOI. All of these 10 cases were heterologous. A single case may report more than 1 EOI. Of these 10 booster dose cases received cumulatively, the Company identified 9 booster dose cases that met case definition for TTS and are stratified by age group and sex and for BC, Centers for Disease Control (CDC), and Pharmacovigilance Risk Assessment Committee (PRAC) criteria.

Literature

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

Rapporteur assessment comment:

TTS was already included in section 4.4 & 4.8 of the SmPC (and the PIL accordingly) and were furthermore evaluated in a signal with EPITT 19689; EMEA/H/C/005737/II/0006/G; and in the MSSRs EMEA/H/C/005737/MEA/014.1 – 07. No additional new information with respect to TTS has occurred during the current reporting interval.

Guillain-Barré Syndrome

Results/Discussion

Primary Dose

During this reporting interval, a total of 12 (6 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting GBS were retrieved. One case was not further discussed since it involved multiple patients with no patient identifiers. The remaining 11 cases (5medically confirmed and 6 medically unconfirmed), all of which were assessed as serious, reported a total of 12 serious EOI. Of the 11 primary dose cases received, the most frequently reported countries/territories of origin (n≥2) were the US (n=3), and Egypt and Germany (n=2 each). These cases concerned 7 males, 3 females, and 1 case did not report sex. Where reported (n=6), the age range was from 20 to 64 years. During the reporting interval, the EOI included Guillain-Barre syndrome (n=10) and chronic inflammatory demyelinating polyradiculoneuropathy (n=2). The mean and median TTO were 203.3 and 113 days, respectively, and the range was from 17 to 480 days. Where reported (n=7), the outcomes of the EOI were reported as follows: not resolved (n=4) and resolving (n=3).

Cumulatively, 679 (388 medically confirmed and 291 medically unconfirmed) primary dose cases reporting GBS were retrieved. Twenty-one cases were not further discussed since these involved multiple patients with no patient identifiers. The remaining 658 cases (369 medically confirmed and 289 medically unconfirmed) were all assessed as serious which reported a total of 696 serious EOI.

Booster Dose

During this reporting interval, no initial case reported as booster was identified.

Cumulatively, 20 (7 medically confirmed and 13 medically unconfirmed) cases reported as booster were identified. Of these cases, there were 19 serious and 1 nonserious case which reported a total of 20 EOI (19 serious; 1 nonserious). Of these 20 cases, 11 were heterologous and 9 were homologous.

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

Venous Thromboembolism

Results/Discussion

Primary Dose

During this reporting interval, a total of 11 serious (2 medically confirmed and 9 medically unconfirmed) primary dose cases reporting VTE were retrieved. All these cases were serious and reported a total of 14 EOI (13 serious; 1 nonserious). Of these 11 primary dose cases received during the reporting interval, the most frequently reported countries/territories of origin were the US (n=4), Germany, Italy and Netherlands (n=2 each), followed by Poland (n=1). Eight of these 11 cases concerned males, and 3 did not report sex. The age range was from 18 to 66 years. During the reporting interval, the most common EOI reported was pulmonary embolism (n=6), followed by deep vein thrombosis (n=4). The mean and median TTO were 759.2 and 646.5 days, respectively, and the range was from 59 to 1375days. Of the 14 EOI, outcomes were reported for 7 and are as follows: not resolved, resolved (n=3 each), and resolving (n=1).

Cumulatively, 2,493 (1,764 medically confirmed and 729 medically unconfirmed) primary dose cases reporting VTE were retrieved. There were 2,355serious and 138 nonserious cases, which reported a total of 3,182 EOI (2,994 serious, 188 nonserious).

Booster Dose

During this reporting interval, a total of 4 (2 medically confirmed and 2 medically unconfirmed) initial cases reported as booster were retrieved. All 4 cases were serious and reported a total of 4 EOIs (all serious). All 4 cases were homologous. Of these 4 cases reported as booster during the reporting interval, the countries/territories of origin reported were Germany, Italy, Netherlands, and the US (n=1 each). These cases concerned 2 males and 2 females. The age range was from 23 to 60 years. During the reporting interval, the EOI included pulmonary embolism (n=2); deep vein thrombosis, and cerebral venous sinus thrombosis (n=1 each). Both mean and median for TTO were 615.5days and the range was from 331 to 900 days. Of the 4 EOI, outcomes were reported for 3 EOI and are as follows: not resolved (n=2) and resolved with sequelae (n=1).

Cumulatively, a total of 113 (77 medically confirmed and 36 medically unconfirmed) cases reported as booster were identified. Of the 113 cases, 96 were serious and 17 were nonserious. These 113 cases reported a total of 138 EOI (119 serious; 19 nonserious). Of these cases, 86 were homologous and 27 were heterologous.

Rapporteur assessment comment

Thromboembolism has been earlier in depth investigated in MEA (EMEA/H/C/005737/MEA/032); as well as in the MSSRs (EMEA/H/C/005737/MEA/014.1-07). MEA 032 resulted in updates of the PI (Section 4.4 and 4.8 of the SmPC and the PIL accordingly).

There is no additional new safety concern detected with VTE during this reporting interval.

Myocarditis and Pericarditis

Results/Discussion

Primary Dose

During this reporting interval, a total of 13 (4 medically confirmed and 9 medically unconfirmed) initial, primary dose cases reporting myocarditis and pericarditis were retrieved. All these serious cases reported 14 serious EOI. In these 13 initial, primary dose cases received, the most frequently reported countries/territories of origin were Brazil, Italy and the US (n=2 each). These cases concerned 5 females, 5males, and 3 cases that did not report sex. The age range was from 22 to 50 years. The EOI reported during the reporting interval included myocarditis (n=10) and pericarditis (n=4). The mean and median TTO were 543.2 and 714 days, respectively, and the range was from 0 to 805days. Where reported (n=7), the outcome for the EOI were as follows: not resolved (n=3), resolving (n=2), fatal (n=1), and resolved (n=1).

Cumulatively, 481 (277 medically confirmed and 204 medically unconfirmed) primary dose cases reporting myocarditis and pericarditis were retrieved. All cases were serious and reported a total of 505serious EOIs. A single case may report more than 1 EOI.

Booster Dose

During this reporting interval, a total of 3 (2 medically confirmed and 1 medically unconfirmed) cases reported as booster were identified. All these serious cases reported 4 serious events of interest. All 3 cases were homologous. In these 3 cases reported as booster, the reported countries/territories of origin were Lithuania (n=2), fol lowed by the US (n=1). These cases concerned 2 males, and 1 female. Where

reported (n=2), the age was 19 years and 49 years. The EOI reported during the reporting interval were myocarditis (n=3) and pericarditis (n=1). The mean and median TTO was 0 (same day). Where reported (n=2), the outcome for the EOI were as follows: resolved (n=1) and resolving (n=1).

Cumulatively, 45(19 medically confirmed and 26 medically unconfirmed) cases reported as booster were retrieved. All these serious cases reported 51 serious EOI. Of these cases, 22 were heterologous and 23 were homologous. A single case may report more than 1 EOI.

Rapporteur assessment comment

Myocarditis and pericarditis were included in both section 4.4 and 4.8 in the SmPC. No additional safety information regarding these items was detected here.

Thrombocytopenia (Including Immune Thrombocytopenia)

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

	Platelet	Treatment	Antiplatelet Autoantibody Test	Causes of Thrombocytopenia (Clinical Manifestations)
Confirmed	A platelet count <100x10⁹/L, with the exclusion of other causes of thrombocytopenia AND a low platelet count nadir (<20x10⁹/L)	AND a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	AND a positive antiplatelet autoantibody test	(Exclusion of other causes of thrombocytopenia)
Likely	A platelet count <100x10⁹/L OR a low platelet count nadir (<20x10⁹/L)	OR a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	OR a positive antiplatelet autoantibody test	AND with the exclusion of other causes of thrombocytopenia
Suspect	-	-	-	Reported thrombocytopenia without a reported underlying or associated cause
Excluded	-	-	-	No thrombocytopenia secondary to other disease (eg, tumour)

Key: ASH American Society of Haematology; IVIG Intravenous Immunoglobulin

Results/Discussion

Primary Dose

During this reporting interval, a total of 11 (9 medically confirmed and 2 medically unconfirmed) initial, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. These 11 serious cases reported a total of 11 serious EOIs. Out of these 11 cases, 2 cases were assessed as ITP cases per ASH case definition. Of the 2 cases received and included for review during the reporting interval, the countries/territories of origin were Spain and US (n=1 each). These cases concerned 2 females, one that was [redacted] years old and the other did not report age. The EOIs reported during the reporting interval included immune thrombocytopenia (n=2). The TTO was not reported in these 2 cases. Of the 2 events, outcomes were reported as resolving (n=1), and unknown (n=1).

Cumulatively, 1,805 (1,572 medically confirmed and 233 medically unconfirmed), primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. There were 854 serious and 951 nonserious cases, which reported a total of 1972 EOI (930 serious, 1042 nonserious). Out of 1,805cases, 550 cases were assessed as ITP cases per ASH case definition.

Booster Dose

During this reporting interval, 1 initial medically confirmed case reported as booster was identified. This case concerned multiple unidentifiable patients and provided limited information regarding the individual patient identifiers which precluded an adequate medical assessment. Hence, this case was not considered for further discussion.

Cumulatively, 287 (276 medically confirmed and 11 medically unconfirmed) cases reported as booster were identified. There were 29 serious and 258 nonserious cases, which reported a total of 289 EOIs (24serious and 265nonserious). Out of 287 cases, 89 cases were assessed as ITP cases per the ASH case definition.

Rapporteur assessment comment:

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

New Information on Important Potential Risks

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

Results/Discussion

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during this reporting interval.

Cumulatively, 1 medically confirmed, post-marketing, primary dose case reporting VAED, including VAERD was retrieved from the search. This case reported 1 serious EOI of antibody-dependent enhancement, and the outcome was not reported.

Booster Dose

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

Rapporteur assessment comment:

No new safety concern is detected here.

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

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

2.4. Adverse Events of Special Interest

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval and cumulatively. After the DLP of the last PBRER (24 February 2024), the Company has not been able to receive further exposure data from various countries/regions. Similarly, the Company cannot perform further RWE rapid cycle analysis following the

withdrawal from the US prior to the reporting interval. Therefore, the Company cannot perform an Observed/Expected analysis.

Cardiac Disorders

Cardiomyopathy

Results/Discussion

Primary Dose

During this reporting interval, a total of 2 medically unconfirmed, initial primary dose cases reporting cardiomyopathy were retrieved. Both cases were serious and reported a total of 2 serious EOI. The 2 primary dose cases retrieved during the reporting interval were reported from Slovak Republic and Germany. These cases concerned 1 male and 1 female, aged [redacted] and [redacted] years, respectively. The EOI included ejection fraction decreased and stress cardiomyopathy (n=1 each). Where reported, the TTO was 426 days (n=1). The outcome of 1 EOI was resolving and the outcome of the other EOI was not reported.

Cumulatively, 87 (57 medically confirmed and 30 medically unconfirmed) primary dose cases reporting cardiomyopathy were retrieved. One case was excluded from further discussion since it involved multiple patients with no patient identifiers. Of the remaining 86 cases (57 medically confirmed and 29 medically unconfirmed), there were 85 serious and 1 nonserious case which reported a total of 95 EOI (91 serious; 4 nonserious). A single case may report more than 1 EOI.

Booster Dose

During this reporting interval, no initial case reported as booster was identified.

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

Literature ICSR

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

Line Listings

Of the 2 primary dose cases received in this interval, the missing information on medical history/concurrent conditions, concomitant medications, clinical course, treatment, and outcome precluded meaningful causality assessment. Where reported, the TTO was 426 days. No literature articles were identified during the interval. Overall, no specific patterns among cases reporting cardiomyopathy were identified.

MAH Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 91 case reports of Cardiomyopathy have been received by the Company, of which 12 had a fatal outcome. However, based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Cardiomyopathy.

Rapporteur assessment comment:

No new safety concern is detected here.

Nervous System Disorders

Encephalitis, Including Acute Disseminated Encephalomyelitis (ADEM) and Meningoencephalitis

Encephalitis, including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis is listed as an AESI in the cRMP.

Results/Discussion

Primary Dose

During this reporting interval, a total of 3 (1 medically confirmed and 2 medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All cases were assessed as serious which reported a total of 3 serious EOI. The 3 primary dose cases retrieved during the reporting interval were reported from Poland, Latvia, and Germany. These cases concerned 2 males, and 1 case did not report sex. The age range was from 25to 37 years. The EOI during the reporting interval, included acute disseminated encephalomyelitis, myelin oligodendrocyte glycoprotein antibody-associated disease, and encephalomyelitis (n=1 each). Where reported (n=1), the TTO was 689 days. The outcomes of the EOI were reported as follows: resolved with sequelae, resolving, and not resolved (n=1 each).

Cumulatively, 108 (75 medically confirmed and 33 medically unconfirmed) primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. Six cases were excluded from further discussion since these involved multiple patients with no patient identifiers. Of the remaining 102 cases (69 medically confirmed and 33 medically unconfirmed), all cases were assessed as serious which reported a total of 108 serious EOI. A single case may report more than 1 EOI.

Booster Dose

During this reporting interval, no initial case reported as booster was identified.

Cumulatively, 3 (2 medically confirmed and 1 medically unconfirmed) cases reported as booster were retrieved. All cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were homologous and 1 was heterologous.

Literature ICSR

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

MAH Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 105 case reports of encephalitis, including ADEM and meningoencephalitis have been received by the Company, of which 07 had a fatal outcome. Based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Encephalitis, including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis.

Rapporteur assessment comment:

Encephalitis has been repeatedly investigated in earlier PSURs. No new information or safety concern is detected during this reporting interval.

Multiple Sclerosis (Including Optic Neuritis)

Results/Discussion

Primary Dose

During this reporting interval, 1 medically confirmed, initial primary dose case reporting multiple sclerosis, including optic neuritis, was retrieved. This serious case was reported for a [redacted]-year-old female from Poland and reported a serious EOI of multiple sclerosis relapse. The TTO was reported as 0 day (same day). The outcome was not reported.

Cumulatively, 88 (46 medically confirmed and 42 medically unconfirmed), primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 88 cases were serious and reported a total of 92 serious EOI. A single case may report more than 1 EOI.

Booster Dose

During this reporting interval, no cases reported as booster were identified.

Cumulatively, 10 (4 medically confirmed and 6 medically unconfirmed) cases reported as booster were identified. All 10 cases were serious and reported a total of 12 serious EOI. Of these cases, 7 were heterologous and 3 were homologous. A single case may report more than 1 EOI.

Literature ICSR

During this reporting interval, no ICSR literature cases were received.

MAH Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 98 case reports of Multiple sclerosis, including optic neuritis have been received by the Company, of which 02 had a fatal outcome. Based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Multiple sclerosis, including optic neuritis.

Rapporteur assessment comment:

No new safety concern is detected here.

Narcolepsy

Results/Discussion

Primary Dose

During this reporting interval, a total of 2 medically unconfirmed, initial primary dose cases reporting narcolepsy were retrieved. These 2 nonserious cases reported 2 nonserious EOI. Of the 2 primary dose cases received during the reporting interval, the reported countries/territories of origin were Estonia and Germany (n=1 each). These cases concerned 1 female and 1 male. The age range was from 50 to 55 years. The EOI included sleep disorder (n=2). One case reported Time to Onset (TTO) of 31 days while TTO was not reported in other. Of the 2 EOI, outcome was reported for 1 as not resolved.

Cumulatively, 614 (85medically confirmed and 529 medically unconfirmed) primary dose cases reporting narcolepsy were retrieved. There were 205 serious and 409 nonserious cases which reported a total of 624 EOI (102 serious, 522 nonserious). A single case may report more than 1 EOI.

Booster Dose

During this reporting interval, a total of 3 (1 medically confirmed and 2 medically unconfirmed) cases reported as booster dose were identified. There were 3 serious cases which reported a total of 2 nonserious and 1 serious EOI. All these 3 cases were heterologous. All the 3 cases reported during the reporting interval as booster were reported from Germany (n=3). These cases concerned 2 males while gender was not reported for 1 case. The age was reported in 1 case (59 years) and not reported in the remaining 2 cases. The EOI reported during the reporting interval included sleep disorder (n=3). The mean and median TTO were not applicable as only 1 case reported latency (0 days). Of the 3 EOI, the outcomes were reported for 2 as not resolved (n=2).

Cumulatively, 56 (7 medically confirmed and 49 medically unconfirmed) cases reported as booster were retrieved. There were 21 serious and 35 nonserious cases which reported a total of 56 EOI (8 serious; 48 nonserious). Of these cases, 36 were heterologous and 20 were homologous.

Literature ICSR

During this reporting interval, no ICSR literature cases were received.

MAH Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 670 case reports of Narcolepsy have been received by the Company, of which 04 had a fatal outcome. However, based on the totality of the safety data available to the Company at the time of the vaccine's marketing 134uthorization withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Narcolepsy.

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

Vascular Disorders

Cerebrovascular Events

Results/Discussion

Primary Dose

During this reporting interval, a total of 15(6 medically confirmed and 9 medically unconfirmed) initial, primary-dose cases reporting cerebrovascular events were retrieved. All of these 15 cases were serious and reported a total of 19 EOI (18 serious, 1 nonserious). Of these 15 primary-dose cases received during the reporting interval, the most frequently reported country/territory of origin was the US (n=8). These cases concerned 7 females, 6 males, and 2 cases that did not report sex. The age range was from 18 to 78 years. The EOI reported during the reporting interval at a frequency >2 included cerebrovascular accident (n=9). The mean and median TTO were 121.6 and 110 days, respectively, and the range was from 3 to 537 days. Of the 19 EOI, outcomes were reported for 8 as follows: resolved (n=6), and not resolved (n=2).

Cumulatively, 1,923 (1,205medically confirmed and 718 medically unconfirmed) primary-dose cases reporting cerebrovascular events were retrieved. There were 1,909 serious and 14 nonserious cases which reported a total of 2,456 EOI (2,438 serious; 18 nonserious). A single case may report more than 1 EOI.

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

During this reporting interval, no fatal (primary dose and booster) case was reported in patients ≤40 years of age. A total of 5 non-fatal (4 primary dose and 1 case reported as booster) cases were reported in patients ≤40 years of age.

Of the 5 non-fatal cases, the EOI was outside the 28-day risk window in 2 cases (all primary dose). The remaining 3 cases (2 primary dose cases and 1 booster dose case) lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results.

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting interval did not identify evidence suggestive of cerebrovascular events being causally associated with Ad26.COV2.S.

Booster Dose

During this reporting interval, a total of 3 (1 medically confirmed and 2 medically unconfirmed) cases reported as booster were identified. All of these 3 cases were serious and reported a total of 3 events (all serious). Of these cases, 2 were heterologous and 1 was homologous. Among these 3 cases reported as booster during the reporting interval, the reported country/territory of origin was the US (n=2), followed by Germany (n=1). These cases concerned 2 males, and 1 case that did not report sex. The age range was from 34 to 47 years. The EOI reported during the reporting interval were Cerebral venous sinus thrombosis, Cerebrovascular accident, Embolic stroke (n=1 each). The TTO was reported in one case as 3 days and rest of two cases TTO was not reported. Of the 3 EOI, the outcomes were reported for 2 as not resolved.

Cumulatively, 84 (44 medically confirmed and 40 medically unconfirmed) cases reported as booster were retrieved. There were 82 serious and 2 nonserious cases which reported a total of 111 EOI (108 serious; 3 nonserious). Of these cases, 28 were heterologous and 56 were homologous. A single case may report more than 1 EOI.

Literature ICSR

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

MAH Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 2,007 case reports of Cerebrovascular events have been received by the Company, of which 220 had a fatal outcome. Cerebrovascular events may occur very rarely as a complication of TTS, VTE or ITP following vaccination. However, based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and spontaneous Cerebrovascular events (ischemic or haemorrhagic).

Rapporteur assessment comment:

No new safety concern is detected here.

Death

As per PRAC confirmation received in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (25August 2021 to 24 February 2022) (EMEA/H/C/PSUSA/00010916/202202) dated 29 September 2022: A separate death subsection with interval and cumulative death cases is no longer required to be presented in the report body of this PBRER or in future PBRERs. However, a separate subsection is found in Appendix of this PSUR for those regions requiring this information.

2.5. Characterisation of risks

Rapporteur assessment comment: The safety concerns remain unchanged.

3. Benefit evaluation

Benefit of this vaccine was demonstrated in adults based on the primary efficacy analysis of the pivotal study COV3001, including 19,630 participants who received Ad26.COV2.S and 19,691 participants who received placebo. Vaccine efficacy (adjusted 95% CI) for the co-primary endpoints against molecularly confirmed moderate to severe/critical COVID-19 in participants who were seronegative at time of vaccination was 66.9% (59.03; 73.40) when considering cases from at least 14 days after vaccination and 66.1% (55.01; 74.80) when considering cases from at least 28 days after vaccination. Consistent efficacy was shown across age groups.

Vaccine efficacy (adjusted 95% CI) against severe/critical COVID-19 occurring at least 14 days after a single Ad26.COV2.S dose was 76.7% (54.56; 89.09) and increased to 85.4% (54.15; 96.90) for severe/critical COVID-19 occurring at least 28 days after a single Ad26.COV2.S dose. Vaccine efficacy against severe/critical COVID-19 was consistently high across age groups in adults, regions and countries. However, due to the change in viral strains of SARS-CoV-2, these data do not reflect the efficacy of the vaccine against circulating variants.

There are no new data on efficacy.

During the reporting period the MAH has withdrawn Ad26.COV2.S from the EU market.

4. Benefit-risk balance

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

The vaccine was based on the initial Wuhan strain and were never updated. Serious ADRs were identified post-marketing; occurring at different frequencies including TTS (very rare), venous thromboembolism (rare), ITP (not known), GBS (very rare), myocarditis and pericarditis (not known), transverse myelitis (not known), CLS (not known) and cutaneous small vessel vasculitis (not known), which were reflected in the SmPC/PIL. These observations led to a very limited use of this vaccine within the EU.

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

5. Rapporteur Request for supplementary information

Not applicable.

Global Medical Safety
Janssen Research & Development, LLC
850 Ridgeview Drive
Horsham, Pennsylvania, 19044
USA

Periodic Benefit Risk Evaluation Report

JNJ-78436735 (Ad26.COV2.S) Vaccine

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

PERIOD COVERED BY THIS REPORT:
25 February 2024 to 30 September 2024

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I have reviewed this report and confirm that, to the best of my knowledge, it accurately describes the data available to date:

Harshad Nalgirkar, MBBS
Medical Safety Officer
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Electronic signatures have been applied at the end of the report.

EXECUTIVE SUMMARY

Introduction

This Periodic Benefit Risk Evaluation Report (PBRER) for JNJ-78436735 (Ad26.COV2.S), herein referred to as Ad26.COV2.S, summarises the safety data obtained by the Company from worldwide sources for the reporting interval of 25 February 2024 to 30 September 2024. The content and format of this report follows the International Council for Harmonisation E2C guidelines on the PBRER and Module VII-Periodic Safety Update Reports of the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices, and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan of Coronavirus Disease-2019 (COVID-19 vaccine). The International Birth Date of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021.

Ad26.COV2.S is indicated for active immunisation for the prevention of COVID-19 in adults greater than or equal to 18 years of age. Ad26.COV2.S is supplied as a colourless to slightly yellow, clear to very opalescent single dose suspension, for intramuscular injection. A booster dose (second dose) may be administered as a homologous booster dose intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. A booster dose may also be administered as a heterologous booster following the completion of a primary messenger ribonucleic COVID-19 vaccine, an adenoviral vector-based COVID-19 vaccine, or an inactivated whole virion COVID-19 vaccine. The dosing interval for the heterologous booster dose should be the same as the dosing interval authorised for the booster dose of the vaccine administered for primary vaccination. The indication is as listed in the Company Core Data Sheet (CCDS) and represents the broadest Company-supported use.

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein. Following vaccination, the S protein is expressed and stimulates an immune response. One dose of Ad26.COV2.S contains $5x10^{10}$ virus particles (vp) in 0.5 mL. Ad26.COV2.S is produced in the PER.C6® TetR Cell Line and by recombinant deoxyribonucleic acid technology. Ad26.COV2.S contains genetically modified organisms. Information regarding the pharmacodynamic and pharmacokinetic properties is contained in the appended CCDS.

Ad26.COV2.S contains the following excipients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2 hydroxypropyl-β-cyclodextrin, polysorbate-80, sodium chloride, sodium hydroxide, hydrochloric acid, and water for injections (see Section 1, Introduction).

Worldwide Marketing Authorisation Status

Ad26.COV2.S is authorised in 17 countries/territories worldwide (see Section 2, Worldwide Marketing Authorisation Status).

Exposure

Cumulative Exposure in Clinical Trials

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

Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programmes, and 719,535 subjects to Ad26.COV2.S in the interventional clinical studies sponsored by other organisations/institutions (see Section 5.1, Cumulative Subject Exposure in Clinical Trials).

Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative

A total of 668,495,350 doses of Ad26.COV2.S vaccine were distributed and 53,288,682 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 30 September 2024.

A total of 3,341,710 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 30 September 2024

Interval

A total of 8,432,900 doses of Ad26.COV2.S vaccine were distributed and 653 doses of Ad26.COV2.S vaccine were administered in worldwide from 01 March 2024 to 30 September 2024.

A total of 670 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa from 01 March 2024 to 30 September 2024 (see Section 5.2, Cumulative and Interval Patient Exposure From Marketing Experience).

Summary of the Overall Benefit-Risk Analysis Evaluation

Despite increasing numbers of vaccinated subjects, and the fact that since May 2023 the ongoing SARS-CoV-2 pandemic is no longer considered as a Public Health Emergency of International Concern (PHEIC) (WHO 2023f), SARS-CoV-2 continues to circulate worldwide and remains a public health concern. The emergence of new virulent lineages has fuelled the need for highly effective preventive measures. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S demonstrated high efficacy against severe/critical disease caused by SARS CoV2 and protection against hospitalisation and death in clinical trial settings. Analysis of spontaneous reports of vaccination failure did not show trends for lack of efficacy. Altogether, the totality of data supports that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some emerging variants. Data on booster usage (homologous or heterologous) suggests increased effectiveness in protecting against COVID-19 including some variants of concern and variants of interest.

Increasing experience based on spontaneous/solicited post-marketing reporting of AEs, have led to the identification of SAEs/reactions such as thrombotic thrombocytopenia syndrome, Guillain-Barré syndrome, immune thrombocytopenia, and myocarditis/pericarditis. These risks occur very infrequently, are adequately monitored and do not outweigh the significant benefits of single dose vaccination with Ad26.COV2.S in controlling the global pandemic (see Section 18.2, Benefit-Risk Analysis Evaluation).

Actions Taken and Proposed for Safety Reasons

No significant actions related to safety were taken during the interval covered by this report (see Section 3, Actions Taken in the Reporting Interval for Safety Reasons and Section 19, Conclusions and Actions).

Conclusions

During the interval of this update, no previously unrecognised ADRs with Ad26.COV2.S have been identified. Consequently, there has been no change to the safety sections of the prescribing information or patient information. No further safety actions are warranted.

The Company has decided not to pursue further development of the vaccine, including adapting the vaccine against emerging variants and paediatric usage, considering the evolution of the SARS-CoV-2 pandemic and competitive landscape where access to a variety of COVID-19 vaccines exists. Therefore, the Company has voluntarily withdrawn the marketing authorisation for Ad26.COV2.S in the European Union (EU) region on 09 August 2024 with all doses in the field expired as of 30 September 2024. Continuous PV

activities for Ad26.COV2.S will be performed in accordance with applicable requirements in countries where market licenses remain active (see Section 19, Conclusions and Actions).

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ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronyms/Abbreviations

Ad26.COV2.S	Adenovirus Type 26.Coronavirus 2.Spike
ADEM	Acute Disseminated Encephalomyelitis and Meningoencephalitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event Of Special Interest
AR	Adverse Reactions
BC	Brighton Collaboration
BTI	Breakthrough Infections
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Sciences
COVID-19	Coronavirus Disease-2019
cRMP	Core Risk Management Plan
DLD/DLP	Data-Lock Date (used for the ease of reading/ understanding–synonymous with Data-Lock Point)
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EOI	Events Of Interest
EU	European Union
EUA	Emergency Use Authorisation
FDA	Food and Drug Administration (United States)
FOIA	Freedom of Information Act
GBS	Guillain-Barré Syndrome
GVP	Good Pharmacovigilance Practices
HCW	Health Care Workers
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HR	Hazard Ratio
IBD	International Birth Date
IC	Information Component
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IIR	Important Identified Risk
IM	Intramuscular
IRR	Incidence Rate Ratios
ITP	Immune Thrombocytopenia
KDCA	Korea Disease Control and Prevention Agency
LL	Line Listing
LOE	Lack Of Efficacy/Effectiveness
MAAEs	Medically-Attended Adverse Events
MAH	Marketing Authorisation Holder (Company)
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism Of Action

mRNA	Messenger Ribonucleic Acid
N/A	Not Applicable
NEC	Not Elsewhere Classified
OR	Odds Ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PF4	Platelet Factor 4
PHEIC	Public Health Emergency of International Concern
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term (MedDRA)
RMP	Risk Management Plan
RSA	Republic of South Africa
RSI	Reference Safety Information
RWD/RWE	Real World Data and Real World Evidence
SAE	Serious Adverse Event
SARI	Severe Acute Respiratory Infection
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2 Spike
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class (MedDRA)
TNCC	Test-Negative Control
TTO	Time to Onset
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
VAED	Vaccine-associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VITT	Vaccine-Induced Immune Thrombotic Thrombosis
VOC	Variants of Concern
VOI	Variants of Interest
vp	Virus particles
VTE	Venous Thromboembolism
VUM	Variant Under Monitoring
WHO	World Health Organisation
wt	Wild type
ZEBOV	Zaire Ebola virus

Definitions of Terms

Authorised product	A health authority has granted marketing authorisation for the active substance/ product and the licence is currently active. This may not include countries/territories where the product is available via other means (eg, parallel import, or where the health authority does not have a formal authorisation procedure).
Completed clinical trial	A completed clinical trial is defined as having a final Clinical Study Report (CSR) available at the time of data-lock for this PBRER reporting interval.
Developmental International Birth Date	The date of first approval (or authorisation) to conduct an interventional clinical trial in any country/territory.
Follow-up case	A case for which additional information was received in the interval covered by this PBRER.

International Birth Date	The date of first marketing authorisation for any product containing the active substance granted to any company in any country/territory in the world.
Interventional	Clinical trials that may involve the following elements: • Those that involve the use of a medicinal product outside of the terms of the marketing authorisation (eg, new indications, dosage range, frequency, combinations) • Those that influence the freedom of choice for a specific treatment option by the treating health professional (eg, the assignment of a patient to a particular treatment strategy is decided in advance by the protocol) • Those that clearly involve additional diagnostic and/or monitoring procedures that are not part of routine clinical practice.
Latency	Unless otherwise defined, latency is the time from initiation of therapy to onset of adverse event.
Marketing Authorisation Holder (Company)	The generic term "Company-sponsored study" is used throughout the document in lieu of the term "MAH-sponsored study" as the J&J entity acting as study sponsor or as MAH may be different. The term "MAH-sponsored study" is retained for the appendices to keep the terminology in line with the GVP module VII titles for appendices.
Negative dechallenge	Continued presence of an adverse event after withdrawal of a product.
Negative rechallenge	Signs and symptoms similar to those observed when the product was previously used do not reappear when the product is reintroduced.
Non-interventional	A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for analysis of collected data.
Ongoing clinical trial	An ongoing clinical trial is defined as a trial in which the first Informed Consent Form has been signed, but does not have a final CSR available at the time of data-lock for this PBRER reporting interval, regardless of whether the last patient last visit has occurred.
Post Authorisation Safety Study (PASS)	A project, whether interventional or non-interventional, involving an authorised Janssen/Johnson & Johnson medicinal product in an approved indication and includes any of the following as a primary objective: • To quantify potential or identified risks, eg, to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers; • To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (eg, pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication); • To evaluate the risks of a medicinal product after long-term use; • To provide evidence about the absence of risks; • To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product or the effectiveness of a risk management measure (eg, collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern); • To measure the effectiveness of risk minimisation measures. Note: such guidance does not apply to the measurement of simple process markers (eg, distribution of the tools reaching the target population, assessing clinical knowledge, assessing clinical actions), refer to Guideline on Good Pharmacovigilance Practices (GVP) Module XVI-Guideline on risk minimisation measures: selection of tools and effectiveness indicators.

Positive dechallenge	Partial or complete disappearance of an adverse event after withdrawal of a product.
Positive rechallenge	Reoccurrence of similar signs or symptoms upon reintroduction of a product.
Source	Classification of reporter or case (eg, health care professional, consumer, literature, study).

1. INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER) for JNJ-78436735 (Ad26.COV2.S), herein referred to as Ad26.COV2.S, summarises the safety data obtained by the Company from worldwide sources for the reporting interval of 25 February 2024 to 30 September 2024. The content and format of this report follows the International Council for Harmonisation (ICH) E2C guidelines on the PBRER and Module VII - Periodic Safety Update Reports (PSUR) of the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan (RMP) of COVID-19 vaccine.[1] The International Birth Date (IBD) of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021.

Ad26.COV2.S is indicated for active immunisation for the prevention of COVID-19 in adults greater than or equal to 18 years of age. Ad26.COV2.S is supplied as a colourless to slightly yellow, clear to very opalescent single dose suspension, for intramuscular (IM) injection. A booster dose (second dose) may be administered as a homologous booster dose intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. A booster dose may also be administered as a heterologous booster following the completion of a primary messenger ribonucleic COVID-19 vaccine, an adenoviral vector-based COVID-19 vaccine, or an inactivated whole virion COVID-19 vaccine. The dosing interval for the heterologous booster dose should be the same as the dosing interval authorised for the booster dose of the vaccine administered for primary vaccination. The indication is as listed in the Company Core Data Sheet (CCDS) and represents the broadest Company-supported use.

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein. Following vaccination, the S protein is expressed and stimulates an immune response. One dose of Ad26.COV2.S contains $5x10^{10}$ virus particles (vp) in 0.5 mL. Ad26.COV2.S is produced in the PER.C6® TetR Cell Line and by recombinant deoxyribonucleic acid (DNA) technology. Ad26.COV2.S contains genetically modified organisms. Information regarding the pharmacodynamic and pharmacokinetic properties is contained in the appended CCDS.

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

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

2. WORLDWIDE MARKETING AUTHORISATION STATUS

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

For pragmatic reasons, the data-lock date for the current Ad26.COV2.S PBRER is 30 September 2024 [24 February].

The indications and the approved doses can be found in Section 1, Introduction.

Ad26.COV2. S is authorised in 17 countries/territories worldwide (see Table 1). In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organisation (WHO)[2].

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=17)

Botswana	Ghana[a]	Moldova, Republic Of	Uganda
Brazil	Guinea-Bissau	Sao Tome and Principe	Vietnam[a]
Central African Republic	Lebanon	South Africa	
Comoros	Lesotho[a]	South Korea	
Georgia	Mauritius	Syrian Arab Republic	

Key: Ad26.COV2.S=Adenovirus Type 26.Coronavirus 2.Spike; n=Number of Countries

a: Licenses were active during the PBRER reporting interval, they were subsequently withdrawn (Lesotho 09 October 2024, Vietnam 02 October 2024) or expired (Ghana 01 November 2024) before finalisation of the PBRER.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

No significant actions related to safety were taken during the reporting interval covered by this report.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The CCDS contains the Company Core Safety Information (CCSI). The CCDS in effect at the end of the reporting interval is dated 22 November 2023.

No significant changes were made to the CCDS (ie, CCSI) within the reporting interval.

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

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Overall, an estimated 82,240 healthy subjects have been enrolled in the Ad26.COV2.S Company sponsored clinical programme, of which approximately 68,705 subjects received Ad26.COV2.S (see Table 2). Of these, 667 subjects were exposed to Ad26.COV2.S in the Phase 1 trials,[3]

[2] Janssen COVID-19 vaccine was delisted from WHO EUL on 09 October 2024

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

935 subjects to Ad26.COV2.S in a Phase 1/2a trial,[4] 2,419 subjects to Ad26.COV2.S in the Phase 2 trials,[5] and 64,684 subjects to Ad26.COV2.S in the Phase 3 trials.[6]

Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programmes,[7] and 719,535 subjects[8] to Ad26.COV2.S in the interventional clinical studies sponsored by other organisations/institutions.[9]

Table 2: Estimated Cumulative Subject Exposure From Clinical Trials Completed and Ongoing

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

Note: Number of subjects exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date (30 September 2024).
Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.
A total of 25,878 subjects (506 subjects from Trial VAC31518COV1001; 150 subjects from Trial VAC31518COV2001; 16,047 subjects from Trial VAC31518COV3001; 781 subjects from Trial VAC31518COV3005; 151 subjects from Trial VAC31518COV3006; and 8,243 subjects from Trial VAC31518COV3009) that received a regimen with both Ad26.COV2.S and placebo, subjects are counted for both Ad26.COV2.S and placebo.
Key: N/A=Not Applicable

Table 3 and Table 4 show cumulative subject exposure by age and sex, and by race from completed clinical trials, respectively.

Table 3: Cumulative Subject Exposure to Ad26.COV2.S From Completed Clinical Trials by Age and Sex

Age Range (Years)	Number of Subjects			
	Male	Female	Undifferentiated[a]	Total[b]
12-17	183	146	0	**329**
18-40	10,498	7,744	7	**18,249**
41-64	19,936	17,859	2	**37,797**
65-75	5,605	5036	0	**10,641**
>75	937	752	0	**1,689**

[4] Trial included VAC31518COV1001.
[5] Trials included VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, and VAC31518COV3006.
[6] Trials included VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, and VAC31518COV3009.
[7] Programs included VAC31518COV4006 and VAC31518COV4007.
[8] In previous PBRER erroneously it was reported as 250, 878 instead of 240,888 for Study VAC31518COV3021.
[9] Studies included COV-BOOST (VAC31518COV2009), VAC31518COV2012, VAC31518COV2016 (AUR1-8-341), VAC31518COV3012 (Sisonke [Together]), VAC31518COV3018, VAC31518COV3021 (Sisonke Boost Open-label Study [SISONKE2]), VAC31518COV4012, and DMID 21-0012.

Table 3: Cumulative Subject Exposure to Ad26.COV2.S From Completed Clinical Trials by Age and Sex

Age Range (Years)	Number of Subjects			
	Male	Female	Undifferentiated[a]	Total[b]
Total	**37,159**	**31,537**	**9**	**68,705**

a: The "undifferentiated" column refers to subjects whose sex was reported as "undifferentiated" or "intersex" on the Case Report Form.
b: Data from completed trials as of 30 September 2024.
Completed clinical trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.

Table 4: Cumulative Subject Exposure to Ad26.COV2.S From Completed Clinical Trials by Race

Race Group	Number of Subjects
American Indian or Alaska Native	4,413
Asian	4,028
Black or African American	10,989
Native Hawaiian or Other Pacific Islander	153
White	44,531
Multiple	2,641
Unknown	752
Not reported	1,197
Missing	1
Total[a]	**68,705**

a: Data from completed trials as of 30 September 2024.
Completed clinical trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.

5.2. Cumulative and Interval Patient Exposure From Marketing Experience

Post-approval (non-clinical trial) Exposure

Estimates of exposure are based on the number of delivered doses reported from LYNX Finance and administered doses reported from Centers for Disease Control and Prevention (CDC 2023) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2023) for European Economic Area (EEA) countries/territories, Korea Disease Control and Prevention Agency (KDCA 2023) for South Korea, Ministério da Saúde (Ministério da Saúde 2021) for Brazil, and National Department of Health (NDH 2023) for South Africa.

The vaccine exposure figures described in this section are an overall estimation with some uncertainties regarding the lack of exposure information received from many countries/territories.

Interval Exposure Estimates

The interval subject exposure for the Ad26.COV2.S vaccine during the reporting interval (01 March 2024 to 30 September 2024) is provided in Table 5.

Table 5: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting interval (01 March 2024 to 30 September 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
ROW		
Ghana	8,179,200	NR
Namibia	1,700	NR
Sierra Leone	151,200	NR
South Africa	0	653
Tanzania, United Republic of	100,800	NR
Total[d]	**8,432,900**	**653**

Key: CDC=Centers for Disease Control and Prevention, ECDC=European Centre for Disease Prevention and Control, EEA=European Economic Area; EU=European Union; NDH=National Department of Health; NR=Not Reported; ROW=Rest of World; US=United States

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

b: Number of vaccine doses administered were reported from the NDH for South Africa.

c: As of 09 August 2021, all entities have the ability to update or delete their previously submitted records. The use of this new functionality may result in fluctuations across metrics on the CDC COVID-19 Data Tracker as historical data are updated or deleted. The functionality will also allow for more accurate reporting and improved data quality. All reported numbers may change over time as historical data are reported to the CDC. In addition, the information within the ECDC website stated that, "All data are subject to retrospective correction" which may be a reason for decrease in the cumulative exposure in certain countries/territories. Exposure values were obtained from the most current counts as of 30 September 2024.

d: Number of vaccine dose distributed and administered were not reported for EEA and US region from 01 March 2024 to 30 September 2024

A total of 8,432,900 doses[10] of Ad26.COV2.S vaccine were distributed in worldwide from 01 March 2024 to 30 September 2024.

A total of 653 doses[10] of Ad26.COV2.S vaccine were administered in worldwide from 01 March 2024 to 30 September 2024.

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 30 September 2024 is provided in Table 6.

Table 6: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 30 September 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	1,292,400	368,544
Belgium	629,200	431,825
Bulgaria	1,777,300	531,830
Croatia	1,135,150	205,687
Cyprus	190,500	31,075
Czechia	547,200	414,024

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

Table 6: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 30 September 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Denmark	1,198,800	45,384
Estonia	110,800	79,490
Finland	68,400	NR
France	3,416,300	1,090,907
Germany	7,818,150	3,753,219
Greece	1,521,600	786,508
Hungary	4,309,200	346,000
Iceland[d]	33,500	54,327
Ireland	281,500	241,743
Italy	2,370,000	1,483,508
Latvia	767,800	294,293
Liechtenstein	NR	264
Lithuania[d]	287,200	295,958
Luxembourg	80,200	41,511
Malta	226,800	32,421
Netherlands	2,464,800	750,752
Norway	403,900	7,435
Poland	15,523,300	3,007,456
Portugal[d]	993,600	1,141,885
Romania	4,080,300	2,069,528
Slovakia	475,200	186,679
Slovenia	230,400	135,358
Spain	2,659,000	1,982,248
Sweden	55,200	NR
ROW		
Afghanistan	20,832,050	NR
Algeria	6,508,800	NR
Angola	4,696,050	NR
Antigua and Barbuda	38,400	NR
Bahamas	38,400	NR
Bangladesh	679,750	NR
Belize	148,800	NR
Benin	3,566,400	NR
Bolivia	1,008,000	NR
Botswana	1,346,400	NR
Brazil	41,000,500	4,821,930
Burkina Faso	6,889,250	NR
Burundi	453,600	NR
Cambodia	1,060,100	NR
Cameroon	6,010,250	NR
Canada	168,000	NR
Central African Republic	4,543,500	NR
Chad	11,465,650	NR
Colombia	11,504,800	NR
Congo (Brazzaville)	5,691,800	NR
Congo, (Kinshasa)	22,965,600	NR
Côte D'ivoire	8,145,400	NR
Djibouti	446,400	NR
Egypt	15,513,450	NR
Equatorial Guine	400,800	NR
Ethiopia	43,394,150	NR
Gabon	866,400	NR
Gambia	777,600	NR
Ghana	19,840,800	NR

Table 6: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 30 September 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Grenada	2,400	NR
Guinea	3,388,800	NR
Guinea-Bissau	1,639,200	NR
Guyana	96,000	NR
Haiti	811,200	NR
Jamaica	216,000	NR
Kenya	17,020,250	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR
Lesotho	1,553,850	NR
Liberia	3,271,200	NR
Madagascar	7,209,950	NR
Malawi	6,960,350	NR
Mali	5,332,750	NR
Mauritania	2,964,000	NR
Mauritius	439,200	NR
Mexico	1,350,000	NR
Moldova	302,400	NR
Morocco	302,400	NR
Mozambique	8,989,700	NR
Namibia	678,500	NR
Nepal	3,711,500	NR
Nicaragua	993,600	NR
Niger	7,939,200	NR
Nigeria	75,009,250	NR
Papua New Guinea	1,123,200	NR
Philippines	12,725,650	NR
Rwanda	897,600	NR
Saint Lucia	12,000	NR
Saint Vincent and Grenadines	7,200	NR
Sao Tome and Principe	100,800	NR
Senegal	3,001,500	NR
Sierra Leone	4,802,400	NR
Solomon Islands	100,800	NR
Somolia	2,601,600	NR
South Africa	30,999,200	8,133,509
South Korea	3,411,000	1,515,847
South Sudan	6,856,250	NR
Sudan	22,846,700	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syria (Damascus)	91,200	NR
Syria (North-West)	300,000	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Tajikistan	451,200	NR
Tanzania, United Republic of	34,890,150	NR
Togo	3,074,400	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	23,388,000	NR
Ukraine	1,202,400	NR
Uzbekistan	4,003,150	NR
Vanuatu	43,150	NR

Table 6: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 30 September 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Yemen	1,216,800	NR
Zambia	15,391,050	NR
US	***41,225,650[e]***	***19,007,537***
Total	**668,495,350[f]**	**53,288,682**

Key: CDC=Centers for Disease Control and Prevention, ECDC=European Centre for Disease Prevention and Control, EEA=European Economic Area; EU=European Union; GAVI/COVAX=Global Alliance for Vaccines and Immunization/COVID-19 Vaccine Global Access; KDCA=Korea Disease Control and Prevention Agency; NDH=National Department of Health; NR=Not Reported; PDR=People's Democratic Republic; ROW=Rest of World; US=United States

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

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

c: The information within the ECDC website stated that, "*All data are subject to retrospective correction*" which may be a reason for decrease in the cumulative exposure for administered doses in certain countries/territories. Exposure values were obtained from the most current counts as of 30 September 2024.

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

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

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

A total of 668,495,350 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 30 September 2024.

A total of 53,288,682 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 30 September 2024.

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

The list of countries/territories along with number of homologous Ad26.COV2.S vaccine booster doses for the interval and cumulative period is provided in Table 7.

Table 7: Total Number of Subjects With the Homologous Ad26.COV2.S Vaccine Booster Doses

Country/Territory	Interval	Cumulative
South Africa	670	1,748,814
South Korea[a]	0	27,032
US[b]	0	1,565,864
Total	**670**	**3,341,710**

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

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

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

A total of 670 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa from 01 March 2024 to 30 September 2024.[11]

A total of 3,341,710 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 30 September 2024.[11]

Exposure by Age for Ad26.COV2.S in EEA

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

Post-authorisation use in special populations

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

5.3. Other Post-approval Use

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

6. DATA IN SUMMARY TABULATIONS

Database

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

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

The Cumulative and Interval Summary Tabulations From Post-marketing Sources (PM Tabulations) 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.

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

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

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

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

Primary Dose versus Booster Dose

Primary dose is defined as the first incidence of administration of the vaccine and booster dose is defined as administration of the vaccine after the primary dose. Although the overall tabulations contain all cases and events (primary dose and booster dose), the searches for each topic were conducted separately based on the configuration outputs. Within this PBRER[12], primary dose and booster dose subsections are presented separately for each topic. As such, the counts of each subsection are not additive.

6.1. Reference Information

All events are coded using Medical Dictionary for Regulatory Activities (MedDRA), version 27.0. Caution is advised when comparing current data with those of Ad26.COV2.S PBRERs using earlier MedDRA versions/coding dictionaries.

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

Appendix 2.1.1 and Appendix 2.1.2 contain a cumulative tabulation of serious adverse events (SAE) from Company-sponsored and non-company-sponsored clinical trials, reported from the Developmental International Birth Date to the data-lock date (DLD) of this Ad26.COV2.S PBRER (all protocols and by protocol, respectively). SAEs from all clinical trials are included regardless of causality (ie, related and not related SAEs are included). Protocols which do not report SAEs are not displayed in the outputs.

SAEs from blinded and unblinded clinical trial cases are included. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related reasons (eg, expedited reporting), if applicable. Data have not been unblinded for the specific purpose of preparing the Ad26.COV2.S PBRER. SAEs are organised by protocol number and then

[12] "In this PBRER there is a change in strategy to include all post-marketing/clinical trials/clinical studies together instead of stratifying the section into post-marketing/ JNJ- sponsored and JNJ-supported clinical studies, except for the topic of Vaccine failure, Lack of efficacy/ Effectiveness. Therefore, there will be differences in the case count as compared to previous PBRER."

MedDRA System Organ Class (SOC) in international order for the investigational medicinal product, blinded treatment and comparators (active and placebo).

6.3. Cumulative and Interval Summary Tabulations From Post-marketing Sources

Appendix 2.2 contains cumulative and interval summary tabulations of "suspected adverse reactions" (thereafter called "adverse reactions" [ARs])[13] received cumulatively to the DLD of this PBRER. These ARs are derived from non-interventional post-marketing studies, other solicited sources and spontaneous notification, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities. Appendix 2.2 also displays ARs from special situation cases (eg, pregnancy, off-label use, overdose, medication error) with no additional ARs reported.

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

During the reporting interval, 1,530 serious ARs and 907 nonserious ARs were received from spontaneous sources, and 31 serious ARs were received from non-interventional post-marketing studies and other solicited sources.[14] For the reporting interval of 25 February 2024 to 30 September 2024, the AR count is notably less than the number of the ARs identified from the previous PBRER reporting interval of 25 February 2023 to 24 February 2024 (4,970 serious ARs and 6,620 nonserious ARs). This decrease in number may be due to the lower exposure to the vaccine compared to last reporting interval.

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 (957)
- Nervous System Disorders (367)
- Musculoskeletal and Connective Tissue Disorders (174)
- Gastrointestinal Disorders (102)

[13] As described in ICH-E2D guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.

[14] This does not include interventional clinical trials.

- Cardiac Disorder (100)

Cumulatively, 103,269 serious ARs (101,967 spontaneous, 1,302 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 Company-sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk minimisation measures that were completed or ongoing during the reporting interval.

7.1. Completed Clinical Trials

A "completed clinical trial" is defined as a trial for which a final clinical study report is available at the time of the data-lock for this PBRER reporting interval.

During the reporting interval, 3 Company-sponsored interventional clinical trials (VAC31518COV2004, VAC31518COV3003, and VAC18193RSV2008) of Ad26.COV2.S were completed. The safety summary from these completed clinical trials is presented below:

Trial VAC31518COV2004

This was a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant (second and/or third trimester of pregnancy) subjects aged ≥18 to ≤45 years. In this trial, Ad26.COV2.S was assessed as a single dose in pregnant women who were previously vaccinated with another COVID-19 vaccine regimen or who were vaccine naïve at study entry.

All randomised subjects were analysed by vaccination group, based on prior to baseline vaccinations with COVID-19 vaccines:

- mRNA group: subjects with a previous primary vaccination (2 doses) or homologous booster vaccination with COVID-19 Vaccine, mRNA (BNT162b2) (Pfizer-BioNTech) or COVID-19 Vaccine, mRNA (mRNA-1273) (Moderna).
- Other group: subjects with previous COVID-19 vaccination (excluding mRNA group), irrespective of previous schedule and vaccine (includes heterologous regimens).
- Vaccine-naive group: subjects who had not received a prior COVID-19 vaccination. A booster vaccination with a single dose of Ad26.COV2.S at 5×10^{10} vp was offered. The booster vaccination was administered not earlier than 2 months after administration of the subject's initial Ad26.COV2.S vaccination in the trial.

Of the 67 subjects screened in this trial, a total of 51 subjects received at least 1 dose of the study vaccine (Ad26.COV2.S): 12, 10, and 29 in the mRNA, Other, and Vaccine-naïve groups, respectively. In the Vaccine-naïve group, 13 subjects also received an Ad26.COV2.S booster vaccination. A summary of safety data is presented below:

Safety Summary

Death, Serious Adverse Events, Discontinuations Due to Adverse Events and, Adverse Event of Special Interest, and Medically-Attended Adverse Events

There were no AEs with fatal outcome in adult subjects.

After a single administration of Ad26.COV2.S, SAEs were reported in 4 (33.3%), 2 (20.0%), and 3 (10.3%) subjects in the mRNA, Other, and Vaccine-naïve groups, respectively. Across vaccination groups, gestational hypertension was reported in 2 (3.9%) subjects; other SAEs by PT occurred in at most 1 (2.0%) subject.

One subject in the Other group experienced a Grade 4 SAE of placental insufficiency at 36 days after vaccination during the third trimester of pregnancy, which was considered related to the study vaccine by the investigator and resolved. This event was followed by a Grade 4 SAE of premature baby, which was considered not related to the study vaccine.

No SAEs were reported after the optional booster dose (ie, booster vaccination period) in vaccine-naïve subjects. No subjects discontinued the trial due to an AE.

A suspected AESI of thrombocytopenia was reported in 2 subjects in the Vaccine-naïve group and was considered not to be related to the study vaccine by the investigator for both subjects. None of the subjects had thrombosis and thrombocytopenia reported concomitantly; therefore, there were no suspected AESIs that qualified for TTS assessment, and no cases of TTS were reported in this trial.

After a single administration of Ad26.COV2.S, Medically-Attended Adverse Events (MAAEs) were reported in 6 (50.0%), 2 (20.0%), and 7 (24.1%) subjects in the mRNA, Other, and Vaccine-naïve groups, respectively. None of these events were considered related to the study vaccine by the investigator. In 1 (10.0%) subject in the Other group, a MAAE of pre-eclampsia occurred within 28 days after vaccination (ie, Post-dose 1). No MAAEs were reported after the optional booster dose (ie, booster vaccination period) in the Vaccine-naïve group. None of the MAAEs led to study discontinuation.

Pregnancy outcomes and pregnancy-related AEs

In subjects with pregnancy outcome, a total of 43/47 (91.5%) subjects had a live term birth, and 4/47(8.5%) a live preterm birth. There were neither stillbirths, nor abortions. Delivery complications were reported in 7/47 (14.9%) adult subjects. Pregnancy-related AEs were reported in 4 (50.0%), 2 (40.0%), and 3 (21.4%) subjects after a single administration of Ad26.COV2.S during the second trimester of pregnancy, and in 1 (25.0%), 3 (60.0%), and 1 (6.7%) subjects after a single administration of Ad26.COV2.S during the third trimester of pregnancy, in the mRNA, Other, and Vaccine-naïve groups, respectively.

Neonates/infants

Deaths, Serious Adverse Events, Adverse Events Leading to Study Discontinuation, Adverse Event of Special Interest, and Medically-Attended Adverse Events

Serious adverse events in neonates/infants were followed up from birth until 12 months postpartum.

One (10.0%) neonate/infant from a mother in the mRNA group had an AE of ventricular septal defect (VSD) with a fatal outcome. Upon physical examination, this neonate was diagnosed with VSD 1 day after the neonate's birth and died on Day 106 due to congenital VSD. This event of VSD was not considered related to the mother's study vaccine exposure.

Serious adverse events were reported in 2 (20.0%), 2 (25.0%), and 3 (10.3%) neonates/infants from mothers in the mRNA, Other, and Vaccine-naïve groups, respectively, during the Postnatal Follow-up 1 period. Similar or lower SAE incidences were reported during Postnatal Follow-up periods 2 and 3. Each SAE by PT occurred in at most 1 (2.1%) neonate/infant, except bronchiolitis, which occurred in 2 (4.3%) neonates/infants during the Postnatal Follow-up 2 period. None of the SAEs were considered related to the mother's study vaccine by the investigator. No neonates/infants discontinued the trial due to an AE.

Multisystem Inflammatory Syndrome in Children in neonates/infants was to be considered an AESI in this trial. No cases of multisystem inflammatory syndrome were reported in neonates/infants.

Medically-attended adverse events were reported in 4 (40.0%), 2 (25.0%), and 2 (6.9%) neonates/infants from mothers in the mRNA, Other, and Vaccine-naïve groups, respectively, during the Postnatal Follow-up 1 period, and in 3 (30.0%), 2 (25.0%), and 4 (13.8%) neonates/infants, respectively, during the Postnatal Follow-up 2 period. The most frequently reported MAAEs by PT were bronchiolitis (0 and 4 [8.5%] neonates/infants during the Postnatal Follow-up 1 and 2 periods, respectively), influenza (1 [2.1%] and 2 [4.3%] neonates/infants, respectively), and jaundice neonatal (2 [4.3%] and 0 neonates/infants, respectively). Other MAAEs occurred in at most 1 neonate/infant during the Postnatal Follow-up 1 and 2 periods. None of the MAAEs led to study discontinuation.

Birth Outcomes

In neonates where birth outcome was assessed, 41/46 (89.1%) had a normal birth outcome. Other birth outcomes were low birth weight (mother in the mRNA group), complications (3 cycles of positive pressure ventilation needed after apnea in one term neonate, and transient tachypnea of the newborn in one preterm neonate, both from mothers in the Vaccine-naïve group), and 2 preterm neonates without complications (both from mothers in the Vaccine-naïve group). For 1 preterm neonate, the birth outcome was not reported in the electronic case report form, but a pregnancy outcome and Grade 4 SAE of premature baby was reported for the neonate's mother. Therefore, this preterm neonate was not included in the birth outcome analysis of the neonates, while it was

included in the AE safety analysis of the adults. Note that the neonate who died following an AE of VSD had a normal birth outcome, as this event started 1 day after the neonate's birth.

Overall, the safety and reactogenicity profile of Ad26.COV2.S is considered acceptable in pregnant women after a single dose in women who were vaccine naïve or previously received a COVID-19 vaccine, and after 2 doses when administered to vaccine-naïve women. No unexpected safety concerns were identified.

Trial VAC31518COV3003

This was 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. The primary purpose of this study was to aid in the establishment of end-expiry specifications for the Ad26.COV2.S regimens that were assessed in the Phase 3 efficacy studies. This trial consisted 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 were evaluated. In the sub-trial, additional adult subjects aged 18 to 55 years were enrolled to further characterise the innate, pro-inflammatory, and other relevant (eg, pro thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events.

Of the 4,801 subjects screened in this trial, a total of 1,593 subjects received at least 1 dose of the study vaccine (Ad26.COV2.S) in main and sub study. A summary of safety data is presented below:

Safety Summary

Deaths, Serious Adverse Events, Discontinuation Due to Adverse Events, Adverse Event of Special Interest, and Medically-Attended Adverse Events

Grade 4 SAEs with fatal outcome were reported for 2 subjects:

Drowning was reported for 1 subject in the 9×10^{10} vp group during the first follow-up period (99 days after receiving study vaccination on Day 1; the subject only received one dose of study vaccine). Death for undetermined reason was reported for 1 subject in the 1.25×10^{10} vp group during the third follow-up period (313 days after receiving the second study vaccination on Day 57). Both SAEs were considered by the investigator as not related to the study vaccine.

During the entire trial, SAEs were reported in 2.0% (32/1,593) subjects. The incidence of SAEs was numerically higher in the highest dose (9×10^{10} vp) group (4.5% [13/288]), and similar across the other dose groups (≤1.8%). The majority of SAEs were reported during the follow-up periods.

By PT none of the SAEs were reported in more than 1 subject, except for abortion spontaneous, which occurred in 1 subject each in the 5×10^{10} vp and the 9×10^{10} vp groups.

Three Grade 4 SAEs were reported: suicide attempt in 1 subject in the 2.5×10^{10} vp group, death (for undetermined reason) in 1 subject in the 1.25×10^{10} vp group, and drowning in 1 subject

in the 9×10^{10} vp group. Most other SAEs were Grade 3 in severity. None of the SAEs were considered related to study vaccine by the investigator.

AEs leading to vaccination regimen discontinuation (mainly COVID-19) were reported in 13 subjects: in 0.4% (6/1,593) subjects post-dose 1 and 0.5% (8/1,579) subjects during follow-up 1. The overall incidence of AEs leading to vaccination regimen discontinuation was similar in all dose groups. None of the AEs leading to vaccination regimen discontinuation were Grade 3 or 4 in severity and none were serious. AEs leading to vaccination regimen discontinuation that were considered related to study vaccine by the investigator were reported in 4 subjects: COVID-19 in 1 participant each in the 1.25×10^{10} vp, 2.5×10^{10} vp, and 3.5×10^{10} vp groups and vaccination site erythema in 1 participant in the7×10^{10} vp group.

None of the subjects had thrombosis and thrombocytopenia reported concomitantly; therefore, there were no suspected AESIs that qualified for TTS assessment, and no cases of TTS were reported in this trial.

During the entire trial, MAAEs were reported in 16.1% (256/1,593) subjects. MAAEs were reported in a similar proportion of subjects in all dose groups (ranging from 12.3% [35/285] to 18.8% [54/288]). By PT, the most frequently reported MAAEs were influenza and COVID-19 (each reported in 2.6% [42/1,593] of all subjects).

Overall, the safety and reactogenicity profile of the Ad26.COV2.S vaccine administered as a 2-dose schedule (with the second vaccination 56 days after the first vaccination) in healthy adults was considered acceptable at all doses levels studied (9×10^{10} vp, 7×10^{10} vp, 5×10^{10} vp, 3.5×10^{10} vp, 2.5×10^{10} vp, and 1.25×10^{10} vp). No new safety signals were identified in this trial.

Trial VAC18193RSV2008

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

Of the 215 subjects screened in this trial, a total of 160 subjects received at least 1 dose of the study vaccine (Ad26.COV2.S, or Ad26/protein preF RSV, or Ad26.ZEBOV) in the trial. A summary of safety data is presented below:

Safety Summary

Deaths, Serious Adverse Events, Discontinuation Due to Adverse Events, Adverse Event of Special Interest, and Medically-Attended Adverse Events

There were no deaths during the trial. Two subjects in the Ad26.ZEBOV group had a total of 3 SAEs in the post-dose 1 period. None of the events were considered to be related to study vaccine by the investigator. One participant had depression, and 1 participant had 2 SAEs (end stage renal disease and renal transplant). The latter participant had end stage renal disease at screening/Day 1 which was discovered after randomisation and vaccination in the trial;

this pre-existing condition was identified as a major protocol deviation. The participant subsequently had a renal transplant during the trial. Two subjects, 1 in each of the Ad26.COV2.S and Ad26/protein preF RSV groups had SAEs (ligament injury and umbilical hernia, respectively) during the open label follow-up period.

No subjects discontinued from the trial due to AEs. One subject in the Ad26.ZEBOV group had an unsolicited AE (end stage renal disease; also reported as an SAE) leading to discontinuation of the Day 57 MVA-BN-Filo vaccination but completed the trial.

Three subjects had events (thrombocytopenia/platelet count decreased) which were suspected AESIs; none of the suspected AESIs qualified for assessment by the TTS Adjudication Committee. None of the subjects reported venous thromboembolism or arterial thrombotic events.

- One subject in the Ad26.COV2.S group had 2 suspected AESIs, pseudothrombocytopenia and worsening thrombocytopenia. Pseudothrombocytopenia of Grade 2 severity started on Day 29 and resolved 44 days later; it was not serious and was not considered to be related to study vaccine. Worsening thrombocytopenia of Grade 3 severity started on Day 44 and resolved 29 days later; it was not serious and was considered to be related to study vaccine. Due to an error in the conversion of laboratory units, the platelet counts on Days 44, 47, 54, 57, 59, 61, and 64 were reported to be of Grade 4 severity instead of Grades 1 to 3. The platelet count was reported as within normal range on the next databased assessment (Day 113). There were no clinical signs of thrombosis. The case was diagnosed as pseudothrombocytopenia related to the use of an ethylenediaminetetraacetic acid tube. The case did not fulfil the definition of a TTS and therefore was not adjudicated by the TTS team.
- One subject in the Ad26.COV2.S group had 1 suspected AESI, platelet count decrease (single observation), on Day 29. The event was of Grade 1 severity, resolved 31 days later, was not serious, and was considered to be not related to study vaccine.
- One subject in the Ad26/protein preF RSV group had 1 suspected AESI, thrombocytopenia, on Day 30. The event was of Grade 1 severity, resolved 15 days later, was not serious, and was considered to be related to study vaccine.

No subjects reported AESI during the trial, ie, events that were identified as AESI and assessed following a request from regulatory authorities in previous studies with the Ad26/protein preF RSV vaccine.

Overall, the Ad26.COV2.S, the Ad26/protein preF RSV, and the Ad26.ZEBOV vaccines were generally well tolerated. The Ad26.COV2.S, the Ad26/protein preF RSV, and the Ad26.ZEBOV vaccines all induced insert-specific antibody responses and neutralising antibodies against the Ad26 vector.

7.2. Ongoing Clinical Trials

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

During the reporting interval, no Company-sponsored interventional clinical trial of Ad26.COV2.S was ongoing.

Independent Data Monitoring Committee/Data Safety Monitoring Board

During the reporting interval, no clinical trials were ongoing, hence, Independent Data Monitoring Committee/ Data Safety Monitoring Board is not applicable for this PBRER.

7.3. Long-term Follow-up

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

7.4. Other Therapeutic Use of Medicinal Product

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

7.5. New Safety Data Related to Fixed Combination Therapies

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

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Based on review of the data from Company-sponsored non-interventional studies for Ad26.COV2.S included in this report during the reporting interval, no new information with potential impact to the benefit-risk assessment has been identified (see Appendix 4.2). Summary from RWE studies is presented below:

Real World Evidence Summary for Ad26.COV2.S

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

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

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

At the time of DLD of this PBRER, 240,888 (*erroneously reported in previous PBRER as 250,878*) subjects received Ad26.COV2.S in this study.

In addition, this study evaluated early VE against hospital admissions of a homologous Ad26.COV2.S boost 4 to 6 months after primary vaccination during the Omicron wave (15 November 2021 to 14 January 2022) in healthcare workers in South Africa (Gray 2022).

Vaccine efficacy (95% CI) against COVID-19 hospital admission was 55% (22% to 74%) when evaluated 0 to 13 days after the booster and increased to 74% (57% to 84%) when evaluated 14 to 27 days and 72% (59% to 81%) 1 to 2 months after the booster. These results provide the first evidence of effectiveness against COVID-19 hospital admissions of a homologous Ad26.COV2.S booster given 4 to 6 months after single dose primary vaccination during a period of Omicron variant circulation.

Study VAC31518COV4002

Final results (up to 12 months after vaccination; median follow-up ranging from 243 days to 268 days) are available from this study, which is an observational longitudinal post-authorisation study to assess the effectiveness of a single-dose of Ad26.COV2.S (5×10^{10} vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US.

The VE results in Janssen's large, longitudinal US cohort study demonstrated effective and stable VE for the single-dose Ad26.COV2.S, based on month analysis and -Kaplan Meier plots through the end of September 2022. There have been several other RWE studies that have been recently published by researchers, that evaluate the VE of -single dose Ad26.COV2.S. The RWE findings support and extend the conclusions of the pivotal efficacy trial. The protection against COVID-19 varies between different variants of concern. Single -dose Ad26.COV2.S VE against infection were reported to be lower during Omicron -emerging and Omicron -predominated periods. Fully vaccinated individuals who received a Ad26.COV2.S booster vaccine showed an increase in VE during the Omicron periods as reported in RWE studies. From the available literature, it is confirmed that there was a benefit to homologous or heterologous Ad26.COV2.S booster doses in protecting against COVID-19 related disease, hospitalisations, and deaths, during the Omicron period. Several factors should be considered that may influence measures of VE and limit direct study comparisons between these studies, including different study designs and outcome definitions and systematic differences in study populations such as underlying comorbidities and other risk factors, as well as demographics including socioeconomic factors. Additionally, methodological considerations such as appropriate matching of comparator cohorts, time since vaccination, follow-up times, and several other bias considerations make it difficult to directly compare point estimates for VE across studies. Despite these limitations, results from several of these real-world studies are consistent with the vaccine effectiveness seen with the single dose Ad26.COV2.S in Study VAC31518COV4002 and the booster dose Ad26.COV2.S in Trial VAC31518COV3021.

Study VAC31518COV4004

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

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

Study VAC31518COV4019

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

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

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

9.1.1. Completed Clinical Study

During the PBRER reporting interval, the following 4 interventional clinical studies were completed for Ad26.COV2.S: 1 interventional clinical study (VAC31518COV2012) sponsored by Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand); 1 interventional clinical study (VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by SAMRC; 1 interventional clinical study (VAC31518COV4012) sponsored by National and Kapodistrian University of Athens; University Research Institute of Maternal and Child Health & Precision Medicine; and 1 interventional clinical study (DMID 21-0012) sponsored by NIH.

Trial VAC31518COV2012

This was a Phase 1/2, prospective, multicentre, observer-blind adaptive trial to assess the safety, reactogenicity, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 years of age in Study Part A and Part B. A total of 570 subjects were recruited. Enrolment of groups were open-label allocation and assessor-masked.

Safety Summary

During the entire study period, Grade 1–3 SAEs occurred in 64 (13.8%) of 465 subjects in the safety analysis population: 52 (14.4%) subjects in Arm A1 and 12 (11.5%) in Arm A2). No SAEs were medically assessed as related to the study booster. No SAEs were fatal or resulted in persistent disability or incapacity. The SAEs in 60 subjects resolved completely; in the remaining 4 (0.9%) subjects, the SAEs (pemphigus vulgaris, prostate cancer, herniated lumbar disc and liver cancer) were ongoing at the study cut-off. In 48 (10.3%) subjects, the SAEs were confirmed SARS-CoV-2 infections, for which 6 (1.3%) subjects required hospitalisation; all 48 affected subjects recovered fully. All SARS-CoV-2 infections were mild or moderate except in 1 subject (0.2%), whose infection was classified as severe because they were treated with favipiravir. The individual was treated as an outpatient and recovered after 10 days. Adverse events of special interests occurred in 3 (0.6%) subjects in Arm 1 and all were medically assessed as not related to the study booster. Grade 2 ageusia in the context of SARS-CoV-2 infection occurred in 2 subjects, and resolved within 9 and 10 days, respectively. Grade 3 pemphigus vulgaris occurred in 1 subject 2.5 months after the booster, required hospitalisation and improved. The subject's condition remained stable at the study cut-off. Seven pregnancies occurred during the study, which resulted in 6 normal deliveries at term. These pregnancies were confirmed 2.5 weeks to 9 months after the booster injection. One pregnancy that was confirmed almost 8 months after the booster injection resulted in spontaneous abortion after in vitro fertilisation. Five newborns were healthy; 1 had a minor congenital anomaly (micro-cleft lip, requiring no surgical intervention) that was medically assessed as unrelated to the study booster given to a subject in her first trimester of pregnancy.

Overall, the Ad26.COV2.S booster remained well tolerated with long-term follow-up, with no new safety concerns.

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

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

Safety Summary

The Sisonke 2 study provided a homologous boost at least 6 months after administration of the priming dose of Ad26.COV2.S for healthcare workers enrolled on the Sisonke Phase 3b implementation study.

A total of 2,350 AEs were reported by 2,117 of the 240,888 (0.88%) subjects enrolled; 1,625 of the 2,350 reported events were reactogenicity events and 28 adverse events which met seriousness criteria. No cases of thrombosis and thrombocytopaenia syndrome were reported; all AEs including thromboembolic disorders occurred at a rate below the expected population rates apart from the 1 reported case of Guillain-Barré syndrome.

The Sisonke 2 study demonstrates that two doses of Ad26.COV2.S were safe and well tolerated; and provides a feasible model for national pharmacovigilance strategies for low-and-middle-income settings. During the study, 2 non-COVID-19 related deaths occurred that were deemed not related to vaccination. Thirteen deaths occurred from breakthrough COVID-19 infections that were deemed unrelated.

Refer to Section 8, Findings from Non-interventional Studies, for more information about booster vaccine effectiveness from this study.

Trial VAC31518COV4012

This was a study in subjects >18 years of age to investigate the association of total antibodies, neutralising antibodies, and T-cell responses against SARS-CoV-2 spike protein with epidemiological and clinical parameters in a cohort of vaccinees after initial immunisation with Ad26.COV2.S and boosting with either Ad26.COV2.S or mRNA vaccines. In addition, it investigated the initial antibody response 1 month after immunisation and then followed the antibody kinetics during a 1-year period and the T-cell responses with sequencing to the T-cell repertoire after initial immunisation with Ad26.COV2.S and boosting with either Ad26.COV2.S or mRNA vaccines.

Safety Summary

After the booster dose, the most common local AE for both vaccines was pain (60%, 6/10), while the most common systemic AEs were myalgias (40%, 4/10) after the Ad26.COV2.S vaccine and fatigue (50%, 5/10) after the BNT162b2 vaccine. No SAE was recorded.

Trial DMID 21-0012

This was a Phase 1/2, open-label study in individuals, 18 years of age and older, who were in good health, had no known history of COVID-19 or SARS-CoV-2 infection, and met all other eligibility criteria. This trial was 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 (mRNA1273 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/ Johnson & Johnson).

Safety Summary

In general, homologous and heterologous booster doses of Ad26.COV2.S in subjects primed with Ad26.COV2.S (Group 4E), mRNA-1273 (Group 5E) or BNT162b2 (Group 6E) were safe and well tolerated. There were no deaths and no SAEs related to study product reported. Additionally, there were no AESIs or NOCMCs reported as related to study product and only one MAAE

(Group 5E-vomiting) recorded as related to study product. Local, solicited and unsolicited AEs were largely similar to those reported for the primary EUA vaccine series with 72% of subjects reporting at least 1 local solicited AE and 82% reporting at least 1 systemic solicited AE. The events reported were predictable, with pain predominating as the most common local symptom, and fatigue ranking as the most common solicited systemic event. Chills, headache, and myalgia were reported as frequent solicited systemic symptoms, but most were mild-moderate in nature and resolved by Day 2 following vaccination. Unsolicited AEs related to study product were not common; 19 subjects reported related AEs, the most common of which were dizziness (n=3) and insomnia (n=3).

Between study groups, a slight trend was noted in terms of increased solicited systemic AEs in the mRNA-primed subjects with 78% of Group 5E and 74% of Group 6E reporting at least 1 event compared to 62% of Group 4E subjects. The reverse finding was noted with local solicited AEs, with 61% of Group 5E and 69% of Group 6E reporting at least 1 event compared to 76% of Group 4E subjects. However, the numbers were low and not statistically significant. Throughout the duration of the study, a number of AESIs were reported in other populations as related to EUA SARS-CoV-2 vaccines, including vaccine-induced immune thrombocytopenia and thrombosis with adenoviral-vectored vaccines and myocarditis with mRNA vaccines. All of these reportable findings were included as AESIs in subsequent protocol amendments owing to the adaptive nature of the trial, but no findings were noted in study subjects. Additionally, the single pregnancy that occurred in a trial subject was treated with a therapeutic abortion. It was concluded that homologous and heterologous dosing of Ad26.COV2.S in previously EUA primed subjects was safe and well tolerated.

9.1.2. Ongoing Clinical Studies

During the PBRER reporting interval, 3 interventional clinical studies sponsored by other organisations/institutions were ongoing for Ad26.COV2.S: 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by University Hospital Southampton National Health Service Foundation Trust; 1 interventional clinical study (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute Not for Profit Company; and 1 interventional clinical study (VAC31518COV3018) sponsored by Mayo Clinic.

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

Study COV-BOOST (VAC31518COV2009)

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

At the time of DLD of this PBRER, 2,883 subjects were enrolled, of which 214 received Ad26.COV2.S.

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

Trial VAC31518COV2016 (AUR1-8-341)

This is a Phase 2a, randomised, observer-blind, multicentre study of the safety and immunogenicity of COVID-19 vaccine strategies in HIV-infected and HIV-uninfected adults. A total of 750 evaluable HIV-infected (660) and HIV-uninfected (90) adult subjects meeting all entry criteria (all inclusion and no exclusion criteria) were planned to be enrolled in 3 treatment strategies in 3 subject groups dependent on prior vaccination with a single dose of Janssen (Group 1), 2 doses of Pfizer (Group 2), or no prior COVID-19 vaccination with evidence of prior SARS-CoV-2 infection (Group 3).

At the time of DLD of this PBRER, 231 subjects received Ad26.COV2.S in this study.

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

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

Trial VAC31518COV3018

This is a Phase 3, prospective, open-label clinical trial with 1 randomised arm to evaluate the response of a heterologous additional dose with the Ad26.COV2.S to provide vaccine induced immunity for immunocompromised kidney transplant patients after receiving 2 or more doses of the Pfizer or Moderna COVID-19 vaccine.

At the time of DLD of this PBRER, 55 subjects received Ad26.COV2.S in this study.

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

9.2. Medication Errors

Introduction

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

Methods

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

Results/Discussion

Primary Dose

During this reporting interval, a total of 2 medically unconfirmed, initial, primary dose cases reporting medication errors were retrieved. None of these cases concerned paediatric patients. These 2 cases reported 3 nonserious medication error EOI and are presented below.

Cumulatively, 2,559 (1,835 medically confirmed and 724 medically unconfirmed), primary dose cases reporting medication errors were retrieved. Of these 2,559 cases, 377 concerned paediatric patients which are discussed in Subsection 9.2.1, Paediatric Cases below. The remaining 2,182 cases reported a total of 2,923 EOI (48 serious; 2,875 nonserious) of medication error are presented below.

An overview of these cases is presented in Table 8.

Table 8: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=2,182
Sex	Male	1	718
	Female	1	703
	NR		761
Age (Years)[b]	18 to 35		325
Minimum: NR	36 to 50		309
Maximum:70	51 to 64		358
Mean: NA	≥65	1	189
Median: NA	Adult		41
	Elderly		7
	NR	1	953
Sources	Spontaneous	2	2,132
	Clinical Study (non-interventional, solicited)		13
	Clinical Study (non-interventional, unsolicited)		25
	Clinical Trial		12
Country/Territory[c]	US	2	1,847
	France		74
	Brazil		41
	Germany		38
	Belgium		26
	Poland		21
	Greece		12
	Ireland		12
	Netherlands		11
	Canada		10

Table 8: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=2,182
	South Africa		10
Event Characteristics		**Number of Events=3**	**Number of Events= 2,923**
Seriousness (Event Level)[d]	Nonserious	3	2,875
	Serious		48
Outcome (Event Level)[d]	Resolved		56
	Not resolved		35
	Resolving		5
	Resolved with sequelae		3
	Fatal		4
	NR	3	2,820

Key: EOI=Event(s) of Interest; NA=Not Applicable; NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation could not be calculated for cases reported during current reporting interval as only 1 case reported age and for calculation at least 2 entries are required. Age group was presented for cases where age was not reported.

c: The countries/territories are presented in decreasing order based on cumulative counts. The countries with frequency ≥10 are presented.

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

Both primary dose cases received during the reporting interval were reported from the US. These cases concerned 1 male and 1 female. The age for 1 case was reported as [redacted] years and was not reported for the other case.

The frequency distribution of the MedDRA PTs of interest is presented in Table 9. A single case may contain more than 1 EOI.

Table 9: Frequency of MedDRA PTs of Interest in Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Poor quality product administered		1		713
Product storage error		1	2	597
Expired product administered			4	541
Incorrect route of product administration		1	3	140
Medication error			2	141
Underdose			1	106
Incorrect dose administered			2	103
Inappropriate schedule of			1	96

Table 9: Frequency of MedDRA PTs of Interest in Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
product administration				
Overdose			10	60
Product administration error			2	66
Extra dose administered				50
Product temperature excursion issue				42
Wrong technique in product usage process				29
Product administered at inappropriate site			3	17
Wrong product administered				20

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

a: For the interval (25 February 2024 to 30 September 2024) column, the events were presented in decreasing order based on the event counts of the cumulative.

b: The MedDRA PTs of interest were sorted by decreasing order for the cumulative. A single case may report more than 1 EOI. The events reported with frequency ≥20 were presented.

Of the 2 primary dose cases retrieved during the reporting interval, none reported the PT of Off-label use.

Both primary dose cases retrieved during the reporting interval reported medication errors with harm. These 2 cases reported 12 additional AEs (1 serious; 11 nonserious). During this reporting interval, no relevant cases were identified for medication error without harm, intercepted or potential medication errors.

The frequency distribution of additional AEs reported in cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 10. Most of the AEs were nonserious and presented local and systemic reactogenicity to Ad26.COV2.S.

Table 10: Frequency Distribution of Additional AEs in Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During Interval		Number of Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Headache			12	100
Pyrexia			8	89
Fatigue			12	81
Pain in extremity			8	76
Pain			6	68
Chills			4	66
Injection site pain			4	59
Nausea			5	43
Myalgia			4	37

Table 10: Frequency Distribution of Additional AEs in Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During Interval		Number of Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Dizziness			8	30
Arthralgia			4	31
Dyspnoea			9	20
Insomnia			3	25
Paraesthesia			3	25
Asthenia			4	22
Chest pain			8	17

Key: AE=Adverse Event

a: For the cumulative column, the events were presented in decreasing order. The events reported with frequency ≥25 are presented.

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

During the reporting interval, 11 non-serious additional AEs including anaemia, cardiac disorder, chest discomfort, feeling abnormal, haemoptysis, liver disorder, malaise, mouth haemorrhage, product colour issue, renal disorder, suspected product contamination, and 1 serious additional AE of thrombosis were reported.

Booster Dose

During this reporting interval, a total of 5 (2 medically confirmed and 3 medically unconfirmed), initial cases reported as booster dose were identified. Of these 5 cases, none concerned paediatric patients. Of these 5 cases, there were 4 serious and 1 nonserious case, which reported a total of 5 nonserious medication error EOI.

Cumulatively, 1,104 (296 medically confirmed and 808 medically unconfirmed) cases reported as booster dose were identified. Of these 1,104 cases, 7 concerned paediatric patients and are discussed in the Subsection 9.2.1, Paediatric Cases below. The remaining 1,097 booster cases reported a total of 1,135 mediation error EOI (32 serious; 1,103 nonserious) and are presented below.

An overview of these cases is presented in Table 11.

Table 11: Characteristics of Selected Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=5[a]	Number of Cases Received Cumulatively=1,097
Sex	Male	2	515
	Female	1	535
	NR	2	47
Age (Years)[b]	18 to 35		218
Minimum: 52	36 to 50		269
Maximum: 59	51 to 64	2	190
Mean: 55.5	≥65		159
Median: 55.5	Adult		7
	Elderly		3
	NR	3	251
Sources	Spontaneous	5[c]	771
	Clinical study (non-interventional, solicited)		326
Country/Territory[d]	US		462
	Brazil		423
	Germany	4	44
	Canada		37
	Korea, Republic of		23
	South Africa		21
	Colombia		21
	Greece		13
Classification	Heterologous	5	411
	Homologous		686
Event Characteristics		**Number of Events= 5**	**Number of Events= 1,135**
Seriousness (Event Level)[e]	Nonserious	5	1,103
	Serious		32
Outcome (Event Level)[e]	Resolved		9
	Not resolved		5
	Fatal		3
	Resolving		1
	NR	5	1,117

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculations were based on the current reporting interval (25 February 2024 to 30 September 2024).

c: This count included 1 case from literature source.

d: The countries/territories are presented in decreasing order based on cumulative counts. The countries with frequency ≥10 are presented.

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

Of these 5 cases reported as booster dose received during the reporting interval, the most frequently reported countries/territories of origin were Germany (n=4), followed by the Spain (n=1). These cases concerned 2 males, 1 female, and 2 did not report sex. The age range was from

52 to 59 years.

The frequency distribution of the MedDRA PTs reported in cases reported as booster is presented in Table 12. A single case may contain more than 1 EOI.

Table 12: Frequency of MedDRA PTs in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Inappropriate schedule of product administration				878
Underdose			1	73
Interchange of vaccine products		5	27	21
Expired product administered				31
Incorrect dose administered				22
Poor quality product administered				19
Product use in unapproved indication				14
Product storage error				13
Medication error				9
Incorrect route of product administration				5
Wrong product administered			1	3
Wrong technique in product usage process				4
Drug delivery system malfunction			1	2
Extra dose administered				3
Product administration error				2
Incorrect product formulation administered				1
Overdose			1	
Product use complaint				1
Product use issue				1
Syringe issue				1
Vaccination error			1	

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

a: For the interval (25 February 2024 to 30 September 2024) column, the events were presented in decreasing order based on the cumulative event counts.

b: The MedDRA PTs of interest are sorted by decreasing order for the cumulative counts. A single case may report more than 1 EOI.

As displayed in Table 12, the reported MedDRA PT of interest for the current reporting interval was Interchange of vaccine products (n=5). All the 5 cases reported as booster dose, contained additional AEs (classified as medication errors with harm). During this reporting interval, no

relevant cases were identified for medication error without harm, intercepted or potential medication errors.

The frequency distribution of additional AEs reported in the reporting interval cases is presented in Table 13. The most frequently reported events were nonserious and represented local and systemic reactogenicity to Ad26.COV2.S..

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

Additional AEs	Number of Events Received During the Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Pyrexia		1	1	202
Headache	1	3	3	175
Pain	1		4	125
Fatigue	1	3	2	114
Myalgia				104
Chills		1		101
Pain in extremity		2	4	70
Injection site pain				67
Dizziness	1	2	1	60
Nausea			2	57
Arthralgia		2	2	51
Malaise			2	50
Asthenia	1	2	4	46
Diarrhoea			2	47
Dyspnoea			2	45
Chest pain			1	45
COVID-19			18	22
Vaccination site pain		1		40

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

a: For the interval (25 February 2024 to 30 September 2024) column, the events were presented in decreasing order based on the event cumulative column.

b: The AEs with a frequency ≥40 have been presented and sorted by decreasing order for the cumulative. A single case may report more than 1 EOI.

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

9.2.1. Paediatric Cases

Primary Dose Case

During this reporting interval, no initial primary dose cases reporting medication errors in the paediatric population were retrieved.

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

399 nonserious).

An overview of these cases is presented in Table 14.

Table 14: Characteristics of Cumulative Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Case Characteristics		Number of Cases Received During Reporting Interval=0	Number of Cases Received Cumulatively=377
Sex	Male		192
	Female		132
	NR		53
Age (Years)[a]	0 to 4		2
Minimum: NA	5 to 10		2
Maximum:NA	11 to 17		354
Mean: NA	Child		6
Median: NA	Adolescent		13
Sources	Spontaneous		373
	Clinical study		4
Country/Territory	US		172
	Latvia		102
	Colombia		41
	Portugal		12
	Germany		8
	France		5
	Romania		4
	Austria		3
	Belgium		3
	Bulgaria		3
	Canada		3
	Croatia		3
	Greece		3
	South Africa		3
	Spain		3
	Poland		2
	Brazil		1
	Estonia		1
	Iceland		1
	Ireland		1
	Netherlands		1
	Philippines		1
	Switzerland		1
Event Characteristics		**Number of Events Reporting During Reporting Interval=0**	**Number of Events Cumulatively=406**
Seriousness (Event Level)[b]	Nonserious		399
	Serious		7

Table 14: Characteristics of Cumulative Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Case Characteristics		Number of Cases Received During Reporting Interval=0	Number of Cases Received Cumulatively=377
Outcome (Event Level)[b]	Not resolved		1
	Resolved		1
	NR		404

Key: EOI=Event(s) of Interest; NA=Not Applicable; NR=Not Reported; US=United States
a: Since no cases were reported during the interval, the mean and median age are not applicable.
b: 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 paediatric cases is presented in Table 15.

Table 15: Frequency of MedDRA PTs of Interest in Cases Reporting Medication Errors in the Paediatric Population With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported in Current Interval		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age			3	345
Product use issue				21
Underdose				10
Medication error			1	4
Vaccination error				4
Wrong product administered				4
Poor quality product administered				4
Accidental exposure to product			2	1
Product use in unapproved indication				2
Expired product administered				2
Circumstance or information capable of leading to medication error			1	0
Product storage error				1
Incorrect dose administered				1
Grand Total			**7**	**399**

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

The frequency distribution of additional AEs reported in the cumulative cases is presented in Table 16. The most frequently reported events were nonserious and represented local and systemic reactogenicity to Ad26.COV2.S.

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

Additional AEs	Number of Events Received During Interval		Number of Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Pyrexia			2	45
Headache				41
Pain in extremity				24
Chills			1	14
Fatigue				12
Malaise			1	8
Pain			1	7
Nausea				7
Myalgia			1	5
Injection site pain				6
Dizziness				5

Key: AE=Adverse Event
a: The MedDRA PTs of interest were sorted by decreasing order for the cumulative. The AEs with frequency ≥5 are presented.

Paediatric Booster Cases

During this reporting interval, no initial booster cases reporting medication errors in the paediatric population were retrieved.

Cumulatively, 7 (4 medically confirmed and 3 medically unconfirmed) cases reported as booster which reported medication errors in paediatric population were identified. Of these 7 cases, 1 was serious and 6 were nonserious, which reported a total of 10 EOI (all nonserious) of medication error.

An overview of the cumulative cases is presented in Table 17.

Table 17: Characteristics of Cumulative Booster Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors in the Paediatric Population

Case Characteristics		Number of Cases Received During Interval=0	Number of Cases Received Cumulatively=7
Sex	Female		4
	Male		3
Age (Years)[a] **Minimum: NA** **Maximum: NA** **Mean: NA** **Median: NA**	0 to 4 5 to 10 11 to 17		7
Sources	Spontaneous		6
	Clinical study (non-interventional, solicited)		1
Country/Territory	Brazil		4
	Canada		1
	Poland		1
	US		1

Table 17: Characteristics of Cumulative Booster Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors in the Paediatric Population

Case Characteristics		Number of Cases Received During Interval=0	Number of Cases Received Cumulatively=7
Event Characteristics		**Number of Events=0**	**Number of Events=10**
Seriousness (Event Level)[b]	Nonserious		10
Outcome (Event Level)[b]	NR		10

Key: EOI=Event(s) of Interest; NA=Not Applicable;NR=Not Reported; US=United States
a: Since no cases were reported during the interval, the mean and median age are not applicable.
b: 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 paediatric cases is presented in Table 18.

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

MedDRA PTs	Number of Events Reported During Interval		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age				7
Inappropriate schedule of product administration				1
Incorrect route of product administration				1
Poor quality product administered				1
Grand Total				**10**

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

The frequency distribution of additional AEs reported in the cumulative cases is presented in Table 19. The most frequently reported events were nonserious and represented local and systemic reactogenicity to Ad26.COV2.S.

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

Additional AEs	Number of Events Received During Interval		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache				2
Abdominal pain upper			1	
Alopecia areata				1
Application site discolouration				1
Arrhythmia			1	
Axillary mass				1
Depressed mood				1
Fatigue				1

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

Additional AEs	Number of Events Received During Interval		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Muscle spasms			1	
Myocardial ischaemia			1	
Nausea			1	
Pyrexia			1	
Renal failure			1	
Vomiting			1	

Key: AE=Adverse Event

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.1.1 and Appendix 6.1.2, respectively.

Discussion

During the reporting interval, there were less number of cases with the medication errors (singular errors) reported for primary dose, while in booster dose cases errors of interchange of vaccine products were reported. No cases reporting medication errors in paediatric population were retrieved during the reporting interval for primary and booster doses.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 3,663 case reports of medication errors (including use in paediatric subjects) have been received by the Company. No new safety issues were identified through review of cases reporting medication errors including paediatric cases. Overall, no new patterns of cases reporting medication errors or potential medication errors were identified. The CCDS contains information for the provider on indication, proper administration, and storage of the vaccine. .

10. NON-CLINICAL DATA

During the reporting interval, no non-clinical studies were conducted for Ad26.COV2.S.

11. LITERATURE

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

The Company focuses the evaluation of the literature references yielded from these searches on new and significant safety findings for previously known safety concerns, as well as unidentified safety and/or efficacy concerns from other safety topics. Published literature generated from MAH sponsored interventional clinical trials retrieved from these searches are not included in this section as any new, important findings are evaluated as part of the clinical trial programme and are included in Section 7, Summaries of Significant Findings From Clinical Trials During the Reporting Interval of this PBRER or have been included in Section 7 in a previous PBRER. Similarly, any literature references that meet ICSR criteria are entered into the Company global safety database and are evaluated in Section 15, Overview of Signals: New, Ongoing, or Closed and Section 16.3, Evaluation of Risks and New Information of the PBRER for any new or significant safety findings that may impact safety topics. Unless additional safety information (apart from ICSR) is included, these literature references are not presented in this section of the PBRER.

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

Selected references and Sponsor Comments are presented below.

11.1. Product-specific Literature

Kim HJ, Kim MH, Park SJ, Choi MG, Chun EM. Autoimmune adverse event following COVID-19 vaccination in Seoul, South Korea. *J Allergy Clin Immunol*. 2024;153(6):1711-1720.

Background: There is growing evidence that the coronavirus disease 2019 (COVID-19) vaccination can affect the regulation of the immune system, leading to the development of autoimmune diseases. However, the autoimmune adverse events (AEs) after COVID-19 vaccination remain largely unclear.

Objective: We sought to investigate the autoimmune AEs after COVID-19 vaccination from a population-based cohort in South Korea.

Methods: A total of 4,203,887 participants, representing 50% of the population residing in Seoul, were recruited from the National Health Insurance Service database and then divided into 2 groups on the basis of COVID-19 vaccination. The cumulative incidence, hazard ratios (HRs), and 95% CIs of autoimmune AEs were assessed following COVID-19 vaccination.

Results: The incidence of vitiligo has been observed to be significantly higher in the vaccination group compared with the no vaccination group. The cumulative incidence of vitiligo began to show a significant difference starting 2 weeks after vaccination, and it reached 2.2% in the vaccination group and 0.6% in the no vaccination group by 3 months after COVID-19 vaccination. Vitiligo (HR, 2.714; 95% CI, 1.777-4.146) was an increased risk among autoimmune AEs. Furthermore, the risk of vitiligo was the highest for heterologous vaccination (HR, 3.890; 95% CI, 2.303-6.573) compared with using cDNA vaccine (HR, 2.861; 95% CI, 1.838-4.453) or mRNA vaccine (HR, 2.475; 95% CI, 1.607-3.813).

Conclusions: Vitiligo as an autoimmune AE was noted to be substantially higher in the COVID-19-vaccinated group compared with the controls. Therefore, the occurrence of vitiligo could be considered as one of the significant AEs post-COVID-19 vaccination

Company Commentary on Citation: *The authors conducted a large population-based cohort study in a specific region and does not encompass the entire population of South Korea. Of the 2,086,709 subjects remaining in the vaccination group after all exclusion criteria were applied by the authors, a total of 12 subjects received Ad26.COV2.S as a first dose and 9 subjects as a second dose as part a heterologous dosing regimen. No subjects were exclusively administered Ad26.COV2.S. No conclusions regarding Ad26.COV2.S were presented by the authors. Based on the paucity of data for Ad26.COV2.S within a heterologous vaccination regimen, no new safety information regarding vitiligo is detected at this time.*

11.2. Class Effect Literature

Couvillion S,Nakayasu ES,Webb-Robertson B-JM, et al. Associations between SARS-CoV-2 Infection or COVID-19 Vaccination and Human Milk Composition: A Multi-Omics Approach. ***bioRxiv.*****2024.**

The risk of contracting SARS-CoV-2 via human milk-feeding is virtually non-existent. Adverse effects of COVID-19 vaccination for lactating individuals are not different from the general population, and no evidence has been found that their infants exhibit adverse effects. Yet, there remains substantial hesitation among this population globally regarding the safety of these vaccines. Herein we aimed to determine if compositional changes in milk occur following infection or vaccination, including any evidence of vaccine components. Using an extensive multi-omics approach, we found that compared to unvaccinated individuals SARS-CoV-2 infection was associated with significant compositional differences in 67 proteins, 385 lipids, and 13 metabolites. In contrast, COVID-19 vaccination was not associated with any changes in lipids or metabolites, although it was associated with changes in 13 or fewer proteins. Compositional changes in milk differed by vaccine. Changes following vaccination were greatest after 1-6 hours for the mRNA-based Moderna vaccine (8 changed proteins), 3 days for the mRNA-based Pfizer (4 changed proteins), and adenovirus-based Johnson and Johnson (13 changed proteins) vaccines. Proteins that changed after both natural infection and Johnson and Johnson vaccine were associated mainly with systemic inflammatory responses. In addition, no vaccine components were detected in any milk sample. Together, our data provide evidence of only minimal changes in milk composition due to COVID-19 vaccination, with much greater changes after natural SARS-CoV-2 infection.

IMPORTANCE The impact of the observed changes in global milk composition on infant health remain unknown. These findings emphasize the importance of vaccinating the lactating population against COVID-19, as compositional changes in milk were found to be far less evident after vaccination compared to SARS-CoV-2 infection. Importantly, vaccine components were not detected in milk after vaccination.

Company Commentary on Citation: *Use in breastfeeding women is identified as missing information in the product's Core Risk Management Plan (cRMP) (version 8.0, 06 February 2024). Moreover, nothing is reported about any association of the breast milk composition and Covid-19 vaccination in the product's RSIs. The current study found that "[...] compared to the mRNA vaccines, the J&J vaccine elicited the most change in milk composition (13 changed proteins at 3 days). [...] Proteins that changed after both natural infection and the Company vaccine were associated mainly with systemic inflammatory responses." However, "[...] impact on infant health of these changes remains unknown." Nevertheless, the authors stated that "These findings emphasise the importance of vaccinating the lactating population against COVID-19, as compositional changes in milk were found to be far less evident after vaccination compared to SARS-CoV-2 infection." No safety observation is identified at this time.*

Wang JJ, Schönborn L, Warkentin TE, et. al. Antibody Fingerprints Linking Adenoviral Anti-PF4 Disorders. *N Engl J Med*. 2024;390(19):1827-1829.

No abstract available.

Company Commentary on Citation: *Anti-PF4 antibodies were obtained from 4 patients with "VITT-like clinical and laboratory features" after wild-type adenoviral infection. These patients had no history of exposure to adenoviral-based vaccines or heparin (for detailed data see Table S1 of the Supplementary Appendix, (Jing 2024)and the cited references. (Warkentin 2023; Campello 2023; Schönborn 2023)*

The authors performed proteomic analysis on these samples and compared the results with the consensus anti-PF4 antibody fingerprints from patients with classic VITT. They found highly similar amino acid fingerprints in the antigen-binding sites, leading to superimposable molecular structures between the VITT-like anti-PF4 antibodies and those identified in patients with VITT.

The authors concluded that adenovirus, rather than other vaccine constituents, directly or indirectly induces the formation of platelet-activating anti-PF4 antibodies.

It is noted, however, that the specific wild-type adenovirus serotype is not reported, and the authors acknowledged that no antigen inducing the formation of platelet-activating anti-PF4 antibodies has been identified. Additionally, the current work does not include analysis of control (without wild type adenoviral infection) samples, therefore no new safety information identified at this time.

12. OTHER PERIODIC REPORTS

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

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

Although protection with a single dose of Ad26.COV2.S in adults ≥18 years of age, including in adults ≥60 years of age against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries, regions, and emerging SARS-CoV-2 variants, including VOC/VOIs, there was a trend towards a decreased protection against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the trial, and this potentially contributes to the observed decrease, although waning protection of Ad26.COV2.S cannot be excluded. Efficacy results from the end-of-study analysis of the Phase 3 trial VAC31518COV3009, in which an Ad26.COV2.S booster dose was administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increased after a homologous booster dose administered 2 months after the single-dose primary vaccination.

When considering the VE against SARS-CoV-2 variants, including VOCs/VOIs, observed in Trial VAC31518COV3001, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or CIs were wide. Differences were observed in protection against moderate to severe/critical COVID-19. No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI]: 58.9% [43.40; 70.50] at least 28 days after vaccination) for the Alpha VOC and other variants was observed, while the VE estimates

for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<37%). The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). For severe/critical COVID-19, the VE estimates were 61% to 91% across variants with sufficient COVID-19 cases, such as Beta, Gamma VOCs, and Lambda, Mu VOIs. In summary, in the double-blind randomised placebo-controlled trial, a single dose of Ad26.COV2.S provided at least 6 months of protection against severe/critical disease, hospitalisation, and death, with varying degrees of protection against symptomatic disease depending on the variant.

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

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

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

14. LATE-BREAKING INFORMATION

Since the DLD of 30 September 2024, no late-breaking information has been identified regarding Ad26.COV2.S.

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

During the reporting interval, there were no validated safety signals new, undergoing evaluation, or closed for Ad26.COV2.S (see Appendix 3).

15.1. Ongoing Signals

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

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

There have been no Regulatory Authority requests received by the Company to monitor a specific topic that was not considered a confirmed signal.

15.3. Use With Concomitant Vaccination

Introduction

Use with concomitant vaccination is included within the PBRER in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases). This concerns a review of data for a potential safety issue after a subject receives a non-COVID-19 vaccine on the same day as Ad26.COV2.S.

A mixed schedule is defined as the administration of different vaccine types against COVID-19 on different dates. Cases reporting the use of heterologous boosters (mixed schedules) relevant to risks will be discussed in Section 16.3, Evaluation of Risks and New Information and those relevant to specific AESI will be discussed under the relevant AESI subsection within Section 16.3.6, Adverse Events of Special Interest.

One trial to specifically evaluate the co-administration of Ad26.COV2.S with influenza vaccines was conducted (Trial VAC31518COV3005). This was a Phase 3, randomised, double-blind, parallel, multicentre trial to evaluate safety, reactogenicity, and immunogenicity of Ad26.COV2.S co administered with a quadrivalent standard-dose in participants 18 years and above (≥18 to ≤64 years) or high-dose seasonal influenza vaccine in participants 65 years and above compared to administration of each vaccine separately to explore whether Ad26.COV2.S and the influenza vaccines can be administered concomitantly. Overall, the safety and reactogenicity profile of concomitant administration of Ad26.COV2.S and the standard dose or high dose influenza vaccine is considered acceptable.

Methods

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

Results/Discussion

Primary Dose

During this reporting interval, a total of 2 medically unconfirmed (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. Both cases were nonserious cases and reported a total of 7 events (all nonserious).

Cumulatively, 291 (204 medically confirmed and 87 medically unconfirmed) primary dose cases reporting the use with concomitant vaccination were identified. There were 211 serious and 80 nonserious cases which reported a total of 838 events (385 serious, 453 nonserious).

The most frequently reported coadministered vaccine type (cumulatively) was the influenza vaccine (n=223). An overview of these cases is presented in Table 20

Table 20: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=291
Sex	Male	1	144
	Female		141
	NR	1	6
Age (Years)[b]	18 to 35	1	34
Minimum: NA	36 to 50		44
Maximum: NA	51 to 64		84
	≥65		116

Table 20: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=291
Mean: NA **Median: NA**	Adult		3
	Elderly		1
	NR	1	9
Source	Clinical Trial		165
	Spontaneous	1	104
	Clinical Study (non-interventional, solicited)	1	18
	Clinical Study (non-interventional, unsolicited)		4
Country/Territory	US	1	149
	Brazil		29
	Belgium		23
	Netherlands		23
	United Kingdom		18
	Spain		10
	Canada		7
	Germany		7
	France		4
	South Africa		4
	Poland	1	3
	Chile		2
	Colombia		2
	Italy		2
	Portugal		2
	Argentina		1
	Austria		1
	Denmark		1
	Greece		1
	Peru		1
	Romania		1
Event Characteristics		**Number of Events=7**	**Number of Events=838**
Seriousness (Event Level)[c]	Serious		385
	Nonserious	7	453
Outcome (Event Level)[c]	Resolved	6	259
	Not resolved	1	197
	Resolving		143
	Fatal		21
	Resolved with sequelae		18
	NR		200
Concomitant Vaccine Type[d]	Influenza vaccine	1	223
	Tetanus vaccine		23
	Pertussis vaccine		19
	Varicella zoster vaccine	1	19
	Pneumococcal vaccine		18
	Hepatitis B vaccine		18
	Diptheria vaccine		15

Table 20: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=291
	Hepatitis A vaccine	1	7
	Typhoid vaccine	1	5
	Polio vaccine		4
	Rabies vaccine		3
	Rubella vaccine		3
	Broncho-vaxom		2
	Japanese encephalitis vaccine	1	2
	Measles vaccine		2
	Mumps vaccine		2
	Yellow fever vaccine		2

Key: NR=Not Reported; NA=Not Applicable; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on cumulative counts.

b: The median and mean age could not be calculated for cases reported during current reporting interval, as only 1 case reported age and for calculation at least 2 entries are required. Age group was presented for the case where age was not reported.

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

d: Concomitant vaccines with frequency ≥2 were presented and sorted in decreasing order for the cumulative counts. A single case may report more than 1 concomitant vaccine.

In these 2 primary dose cases received during the reporting interval, the reported countries/territories of origin were Poland and the US (n=1 each). One case concerned 1 male and sex was not reported in the remaining case. The reported age in 1 case was 33 years and was not reported in the other case.

The frequency distribution of the MedDRA PTs reported is presented in Table 21

Table 21: Frequency Distribution of MedDRA PTs in Primary Dose Cases Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Headache		1		23
Fatigue			1	21
Pyrexia			1	20
Malaise				15
Pain in extremity			4	11
Vaccination failure			15	
Arthralgia		1	1	13
Chills				12
Osteoarthritis			11	1
Pain			2	10
Injection site pain				10
Pulmonary embolism			9	1
COVID-19			1	8
Dizziness			2	7
Guillain-Barre			8	

Table 21: Frequency Distribution of MedDRA PTs in Primary Dose Cases Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
syndrome				
Myalgia				8
Thrombocytopenia			2	6
Asthenia			1	6
Back pain			2	5
Diarrhoea			1	6
Nausea			1	6
Suspected COVID-19			1	6
Cough			1	5
Exposure during pregnancy			1	5
Prostate cancer			5	1
Vision blurred				6

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

a: The MedDRA PTs with frequency ≥6 have been presented and sorted by decreasing order for the cumulative counts. A single case may report more than 1 MedDRA PT.

The events reported during the reporting interval included alopecia, arthralgia, decreased appetite, headache, injection site ulcer, photosensitivity reaction and vomiting (n=1, each). None of the cases reported TTO for the events. The reported outcomes for the 7 events are as follows: resolved (n=6), and not resolved (n=1). Of the 2 cases, 1 documented coadministration on the same day as Ad26.COV2.S and in the remaining 1 case, the date of vaccination was more than 1 month.

Booster Dose

During this reporting interval, a total of 1 medically unconfirmed initial case reported as booster was identified. This was a nonserious case which reported a total of 3 events (all nonserious). This case was heterologous.

Cumulatively, 112 (22 medically confirmed and 90 medically unconfirmed) cases reported as booster were identified. There were 37 serious and 75 nonserious cases which reported a total of 651 events (99 serious, 552 nonserious). Of these cases, 72 were heterologous and 40 were homologous. The most frequently reported coadministered vaccine type (cumulatively) was the influenza vaccine (n=107).

An overview of these cases is presented in Table 22

Table 22: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=1[a]	Number of Cases Received Cumulatively=112
Sex	Female		55
	Male	1	54
	NR		3
Age (Years)[b]	>18		1
Minimum: NA	18 to 35		13
Maximum: NA	36 to 50		18
Mean: NA	51 to 64		37
Median: NA	≥65		30
	Adult		2
	Elderly		1
	NR	1	10
Source	Spontaneous	1	64
	Clinical Study (solicited, non-interventional)		38
	Clinical Trial		7
	Clinical Study (unsolicited, non-interventional)		3
Country/Territory	US	1	34
	Brazil		32
	Germany		29
	Canada		8
	Netherlands		2
	Portugal		2
	Argentina		1
	Poland		1
	South Africa		1
	Spain		1
	United Kingdom		1
Classification	Heterologous	1	72
	Homologous		40
Event Characteristics		**Number of Events=3**	**Number of Events=651**
Seriousness (Event Level)[c]	Nonserious	3	552
	Serious		99
Outcome (Event Level)[c]	Resolved		187
	Resolving		169
	Not resolved		116
	Fatal		2
	Resolved with sequelae		2
	NR	3	175
Concomitant Vaccine Type[d]	Influenza vaccine	1	107
	Pneumococcal vaccine		4
	Tetanus vaccine		2
	Diphtheria vaccine		1
	Hepatitis A vaccine		1
	HPV vaccine		1
	Meningococcal vaccine		1
	Pertussis Vaccine		1
	RSV vaccine	1	1

Table 22: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=1[a]	Number of Cases Received Cumulatively=112
	Varicella Zoster vaccine		1

Key: HPV=Human Papillomavirus; NA=Not Applicable; NR=Not Reported; RSV=Respiratory Syncytial Virus; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on cumulative counts.

b: The median and mean age calculation could not be calculated for case reported during current reporting interval as for calculation at least 2 entries are required

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

d: Concomitant vaccines were presented in decreasing order for the cumulative counts. A single case may report more than 1 concomitant vaccine.

The only case reported during the current reporting interval was from the US and concerned a male patient of unspecified age.

The frequency distribution of the MedDRA PTs reported in these booster cases is presented in Table 23

Table 23: Frequency Distribution of MedDRA PTs in Cases Reported as Booster and Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Injection site pain				53
Fatigue			2	46
Headache			4	43
Off label use				35
Pyrexia			2	22
Myalgia			1	22
Malaise			1	21
Arthralgia			1	19
Chills			1	15
COVID-19 immunisation				16
Dizziness			1	15
Inappropriate schedule of product administration				15
COVID-19			3	11
Pain in extremity				11
Back pain			1	7
Vaccination failure			8	
Injection site swelling				7
Nausea			1	6
Pain				7
Suspected COVID-19			1	6
Asthenia				6
Feeling abnormal				6
Vaccination site pain				5

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

Table 23: Frequency Distribution of MedDRA PTs in Cases Reported as Booster and Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

Activities; PT=Preferred Term

a: For the interval (25 February 2024 to 30 September 2024) column, the events count were not presented as they did not fall under the PTs presented here. Interval events counts have been presented based on cumulative events.

b: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the cumulative counts. A single case may report more than 1 MedDRA PT.

The reported MedDRA PTs during the interval included Memory impairment, Epistaxis, and Adverse drug reaction (n=1 each). The mean and median TTO were not reported. Event outcome was unspecified for all events. The date of concomitant vaccine administration was not specified in this case.

Literature ICSR

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

Line Listings

Primary and Booster: An interval CIOMS II LL of cases reported as primary, and booster is presented in Appendix 6.2.1. and Appendix 6.2.2.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 403 case reports of concomitant use of Ad26.COV2.S and another vaccines have been received by the Company. The most commonly co-reported vaccine was influenza vaccine. The majority of the adverse events reported in patients receiving Ad26.COV2.S with concomitant vaccines were reactogenic and/or listed for Ad26.COV2.S. No trend or pattern of events was observed. Based on review of all the available data, no further safety measures are deemed necessary.

15.4. Vaccination Anxiety-related Reactions

In the Final Assessment Report (FAR), the PRAC Rapporteur for the Ad26.COV2.S PBRER dated 25 February 2022 to 24 August 2022, circulated on 14 April 2023 (PRAC AR 2023) (procedure number: EMEA/H/C/PSUSA/00010916/202208) indicated that,

"The vaccination stress/anxiety related ADRs are considered well documented and adequately managed in clinical practice, and therefore could be removed from detailed presentation in future PSURs".

This section will not be included within the body of this PBRER and future PBRERs; however, a separate subsection is found in Appendix 6.3 for those markets requiring this information.

15.5. Vaccine Failure, Lack of Efficacy/Effectiveness

Introduction

Vaccine failure, 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 (version 8.0, 06 February 2024) for Ad26.COV2.S based on past experiences in the development of vaccines against the respiratory syncytial virus (RSV), dengue virus, SARS-CoV-1, and Middle East respiratory syndrome-related coronavirus (MERS-CoV).

Confirmed vaccination failure is defined as the occurrence of a specific vaccine-preventable disease in a person who is appropriately and fully vaccinated, taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation. This definition requires clinical confirmation that the disease is specifically targeted by the vaccine (see Appendix 5).

Methods

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

As per the GVP Module on Vaccines (Product or Population-specific Considerations I: Vaccines for prophylaxis against infectious diseases), only spontaneous cases were presented in the Section and information on JNJ-sponsored and JNJ-supported clinical study cases can be found in Section 13, Lack of Efficacy in Controlled Clinical Trials, and Section 17, Benefit Evaluation, of the PBRER.

For the purposes of this analysis, all medically confirmed cases with a TTO >14 days and reporting a Preferred Term (PT) consistent with a COVID-19 diagnosis (Asymptomatic COVID-19, Breakthrough COVID-19, Coronavirus infection, Coronavirus pneumonia, Coronavirus test positive, COVID-19, COVID-19 pneumonia, Loss of therapeutic response, Post-acute COVID-19 syndrome, SARS-CoV-2 RNA increased, SARS-CoV-2 sepsis, SARS-CoV-2 test positive, SARS-CoV-2 viraemia, Vaccine derived SARS-CoV-2 infection, Vaccination failure [except cases where suspected COVID-19 PTs are also reported], and Virologic failure) or laboratory findings of positive polymerase chain reaction (PCR) test confirming COVID-19 positivity were considered as confirmed vaccination failures. Medically confirmed cases with a TTO >14 days and reporting the PT Suspected COVID-19 or a COVID-19 laboratory test PT with no result will be considered as suspected vaccination failures.

Results

Primary Dose

During this reporting interval, a total of 257 (244 medically confirmed and 13 medically unconfirmed) post-marketing, initial, primary-dose cases reporting events of vaccine failure, LOE were identified. There were 251 serious and 6 nonserious cases which reported a total of 265 EOIs (251 serious, 14 nonserious).

Cumulatively, 15,901 (13,309 medically confirmed and 2,592 medically unconfirmed) post-marketing, primary-dose cases reporting events of vaccine failure, LOE were identified. There were 14,033 serious and 1,868 nonserious cases which reported a total of 27,661 (24,616 serious and 3,045 nonserious)

An overview of these cases is presented in Table 24.

Table 24: Characteristics of Post-marketing Primary-dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Interval=257[a]	Number of Cases Received Cumulatively=15,901
Sex	Male	211	8,839
	Female	30	5,674
	NR	16	1,388
Age (Years)[b]	<18		29
Minimum: 18	18 to 35	152	6,644
Maximum: 78	36 to 50	45	4,313
Mean: 33.7	51 to 64	37	2,693
Median: 30	≥65	2	1,074
	Adult	1	62
	Neonate		17
	Infant		10
	Elderly		7
	Foetus		1
	Adolescent		1
	NR	20	1,050
Sources	Spontaneous	248[c]	15,668
	Clinical study (non-interventional, solicited)	8[d]	225
	Clinical study (non-interventional, unsolicited)	1	8
Country/Territory[e]	Austria	1	9,674
	US	14	2,261
	Portugal	226	1,305
	Iceland		853
	Germany	4	414
	Philippines		278
	France		170
	Brazil	1	112
	Greece	2	95
	Lithuania		75
	South Africa		75
	Netherlands	3	72
	Spain	2	69
	Belgium		63
	Estonia		57
	Italy	1	57

Table 24: Characteristics of Post-marketing Primary-dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Interval=257[a]	Number of Cases Received Cumulatively=15,901
	Canada	1	43
	Poland	1	29
	Colombia		24
	Mexico		21
	Czech Republic		18
	Switzerland		14
	Romania		12
	Croatia		10
Event Characteristics		**Number of Events=265**	**Number of Events=27,661**
Seriousness Criteria (Event Level)[f]	Other medically important condition	244	22,898
	Hospitalisation	7	1,550
	Death	3	361
	Life-threatening		302
	Disability		92
	NR	14	3,045
Seriousness (Event Level)[f]	Serious	251	24,616
	Nonserious	14	3,045
Outcome (Event Level)[f]	Resolved	117	1,365
	Not resolved	2	811
	Resolving	31	631
	Fatal	3	361
	Resolved with sequelae		12
	NR	112	24,481

Key: NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). Age at the time of Adverse Event is considered and Age group was presented for cases where age was not reported.

c: Counts included 7 literature cases.

d: Counts included 8 literature cases.

e: The countries reporting cases with frequency ≥10 have been presented and sorted by decreasing order for the cumulative counts.

f: Seriousness criteria, seriousness, and outcome have been presented for the events of interest. A single case may report more than 1 event and 1 event may report with more than 1 seriousness criteria.

Of these 257 cases received during the current interval, the most frequently reported countries/territories of origin (≥3) were Portugal (n=226), the US (n=14), Germany (n=4), and Netherlands (n=3). These cases concerned 211 males, 30 females, and 16 that did not report sex. The age range was from 18 to 78 years when reported.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 25.

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

MedDRA PTs	Number of Events Received During the Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Vaccination failure	58		12,284	
COVID-19	5	13	10,502	1,065
SARS-CoV-2 test positive	1		258	1,158
Suspected COVID-19		1	147	705
Drug ineffective	117		652	3
COVID-19 pneumonia			224	
Therapy non-responder			202	2
Thrombosis with thrombocytopenia syndrome	8		117	
SARS-CoV-2 test negative			75	25
SARS-CoV-2 test			36	13
Therapy partial responder			34	
Post-acute COVID-19 syndrome	1		13	13
Exposure to SARS-CoV-2			16	7
SARS-CoV-2 antibody test negative			8	7
Breakthrough COVID-19	1		4	10
Coronavirus infection			1	9
SARS-CoV-2 antibody test positive			5	5
Therapeutic product effect decreased			5	5

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative count.

b: The MedDRA PTs of interest with a frequency ≥10 have been presented and sorted by decreasing order for the cumulative counts. A single case may report more than 1 MedDRA PT.

During the reporting interval, the EOIs included drug ineffective (n=177), vaccination failure (n=58), COVID-19 (n=18), thrombosis with thrombocytopenia syndrome (n=8) and breakthrough COVID-19, post-acute COVID-19 syndrome, SARS-CoV-2 test positive and suspected COVID-19 (n=1 each), The mean and median TTO were 107.6 days and 106 days, respectively, and the range was from 0 to 1,022 days. Of the 265 EOIs, outcomes were reported for 153 as follows: resolved (n=117), resolving (n=31), fatal (n=3), and not resolved (n=2).

The TTO reported in these 257 cases is presented in Table 26.

Table 26: Time to Onset in Post-marketing Primary-dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Cases=257)

TTO	Number of Cases[a]
≤14 days	9
>14 days but ≤28 days	9
>28 days	210
NR	29
Total	**257**

Table 26: Time to Onset in Post-marketing Primary-dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Cases=257)

TTO	Number of Cases[a]

Key: NR=Not Reported; TTO=Time to Onset
a: One case may report more than 1 event.

Of the total 257 cases received during the interval, 54 medically confirmed cases reported a TTO >14 days and reported PTs consistent with a COVID-19 diagnosis or laboratory finding of positive PCR test confirming COVID-19 positivity. None of the medically confirmed cases with a TTO >14 days reported the PT suspected COVID-19 or a COVID-19 laboratory test PT with no result. Cases and events of confirmed vaccination failure (n=54) are described in Table 27.

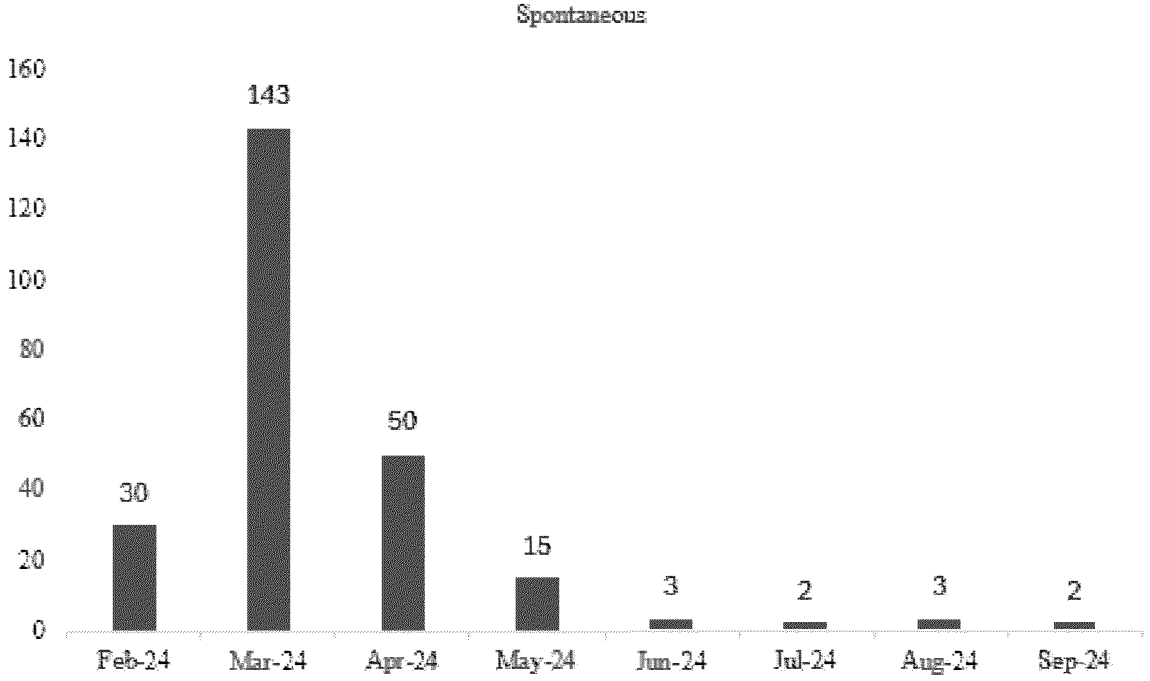
Table 27: Events of Confirmed Vaccination Failure in Post-marketing Primary-dose Cases Involving the Use of Ad26.COV2.S (Cases=54; Events=55)

Confirmed Vaccination Failure (Cases=54)	
Preferred Term	**Number of Events**
Vaccination failure	52
COVID-19	1
Total confirmed COVID-19 events	**55[a]**

Key: COVID-19=Coronavirus Disease-2019; EOI=Event(s) of Interest; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2
a: In addition to events presented above, 2 confirmed cases reported the MedDRA PT Drug ineffective; this event is not presented in the table.

Figure 1 depicts the case count of primary-dose spontaneous cases by month involving the use of Ad26.COV2.S and reporting vaccine failure, LOE from 25 February 2024 to 30 September 2024.

Figure 1: Case Count of Post-marketing Primary-dose Spontaneous Cases by Month Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Interval: 25 February 2024 to 30 September 2024).



Please see the Discussion section below for observations from Figure 1.

The events are further sorted by seriousness and their respective outcomes in Table 28 and Table 29.

Table 28: Serious MedDRA PTs of Interest and Their Outcomes in Post-marketing Primary-dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=251)

MedDRA PTs	Number of Event Outcomes					
	Fatal	Not Resolved	Resolved	Resolving	NR	Total Number of Events[a]
Drug ineffective			86	21	70	177
Vaccination failure		1	28	9	20	58
Thrombosis with thrombocytopenia syndrome[b]			1		7	8
COVID-19	1		1		3	5
SARS-CoV-2 test positive	1					1
Breakthrough COVID-19	1					1
Post-acute COVID-19 syndrome					1	1

Table 28: Serious MedDRA PTs of Interest and Their Outcomes in Post-marketing Primary-dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=251)

MedDRA PTs	Number of Event Outcomes					
	Fatal	Not Resolved	Resolved	Resolving	NR	Total Number of Events[a]

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

a: A single case may report more than 1 MedDRA PT.

b: Additional information included in Section 16.3.1.5, Thrombosis With Thrombocytopenia Syndrome, Thrombosis With Thrombocytopenia Syndrome.

Table 29: Nonserious MedDRA PTs of Interest and Their Outcomes in Post-marketing Primary-dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=14)

MedDRA PTs	Number of Event Outcomes					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events
COVID-19	1	1		1	10	13
Suspected COVID-19					1	1

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

Booster Dose

During this reporting interval, a total of 17 (8 medically confirmed and 9 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 8 serious and 9 nonserious cases which reported a total of 33 EOIs (5 serious, 28 nonserious). Of these cases, 14 were heterologous and 3 were homologous.

Cumulatively, 1,023 (343 medically confirmed and 680 medically unconfirmed) cases reported as booster were identified. There were 574 serious and 449 nonserious cases which reported a total of 1,469 EOIs (654 serious, 815 nonserious). Of these cases, 656 were heterologous and 367 were homologous.

An overview of these cases reporting booster dose is presented in Table 30.

Table 30: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Interval=17[a]	Number of Cases Received Cumulatively=1,023
Sex	Female	2	436
	Male	4	347
	NR	11	240
	18 to 35	2	151

Table 30: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Interval=17[a]	Number of Cases Received Cumulatively=1,023
Age (Years)[b] **Minimum: 23** **Maximum: 59** **Mean: 36.7** **Median: 28**	36 to 50		206
	51 to 64	1	231
	≥65		162
	Infant		2
	Adult		8
	Elderly		7
	NR	14	256
Sources	Spontaneous	16	910
	Clinical study (non-interventional, solicited)	1	88
	Clinical study (non-interventional, unsolicited)		25
Country/Territory[c]	US	10	617
	Brazil	1	78
	Iceland		73
	Canada		57
	Germany	2	52
	Austria		40
	Greece	2	18
	Philippines		17
	France		13
	Spain		12
	Portugal		8
	Belgium		6
	Poland		4
	South Africa		4
	Hungary		3
	Korea, Republic of		3
	Lithuania		3
Event Characteristics		**Number of Events=33**	**Number of Events=1,469**
Seriousness Criteria (Event Level)[d]	Other medically important condition	5	544
	Hospitalisation		103
	Death		21
	Life-threatening		14
	Disability		6
	NR	28	815
Seriousness (Event Level)[d]	Serious	5	654
	Nonserious	28	815
Outcome (Event Level)[d]	Not resolved	3	215
	Resolving	6	145
	Resolved	1	174
	Fatal		21

Table 30: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Reporting Interval=17[a]	Number of Cases Received Cumulatively=1,023
	Resolved with sequelae		4
	NR	23	910

Key: NR=Not Reported; US=United States
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative interval.
b: The median and mean age calculations were based on the current reporting interval. Age group was presented for cases where age was not reported.
c: Countries/territories with frequency ≥3 were presented in decreasing order for the cumulative interval.
d: Seriousness criteria, seriousness and outcome have been presented for the events. A single case may report more than 1 event and 1 event may report more than 1 seriousness criteria.

Of these 17 cases reported as booster during the reporting interval, the reported countries/territories of origin were the US (n=10), Germany and Greece (n=2 each) and Brazil, Italy and Ireland (n=1 each). These cases concerned 4 males, 2 females, and 11 that did not report sex. The age range was from 23 to 59 years when reported.

The frequency distribution of the MedDRA PTs in cases reported as booster is presented in Table 31.

Table 31: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

MedDRA PTs	Number of Events Received During the Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Nonserious	Serious	Nonserious	Serious
COVID-19	8	1	416	117
Vaccination failure		2	1	394
Suspected COVID-19	2		249	29
SARS-CoV-2 test positive	2		119	15
Drug ineffective		1	2	44
Therapy non-responder				19
COVID-19 pneumonia				18
Post-acute COVID-19 syndrome	3		9	1
SARS-CoV-2 test negative			3	5
Thrombosis with thrombocytopenia syndrome		1		8
Breakthrough COVID-19	1		4	1
SARS-CoV-2 antibody test negative			2	1
Therapeutic product effect decreased			1	2
Coronavirus infection			2	
Exposure to SARS-CoV-2			2	

Table 31: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative count.

b: The MedDRA PTs of interest with a frequency ≥2 have been presented. A single case may report more than 1 MedDRA PT.

The EOIs included COVID-19 immunisation (n=12), COVID-19 (n=9), post-acute COVID-19 syndrome (n=3), suspected COVID-19, SARS-CoV-2 test positive and vaccination failure (n=2 each), breakthrough COVID-19, drug ineffective and thrombosis with thrombocytopenia syndrome (n=1 each). The mean and median TTO were 1,010.7 and 1,048 days, respectively, and the range was from 0 to 1,073 days. Of the 33 EOIs, outcomes were reported for 10 as follows: resolving (n=6), not resolved (n=3) and resolved (n=1).

The TTO reported for the 17 cases is presented in Table 32.

Table 32: Time to Onset in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=17)

TTO	Number of Cases[a]
≤14 days	1
>14 days but ≤28 days	
>28 days	5
NR	11

Key: NR=Not Reported; TTO=Time to Onset

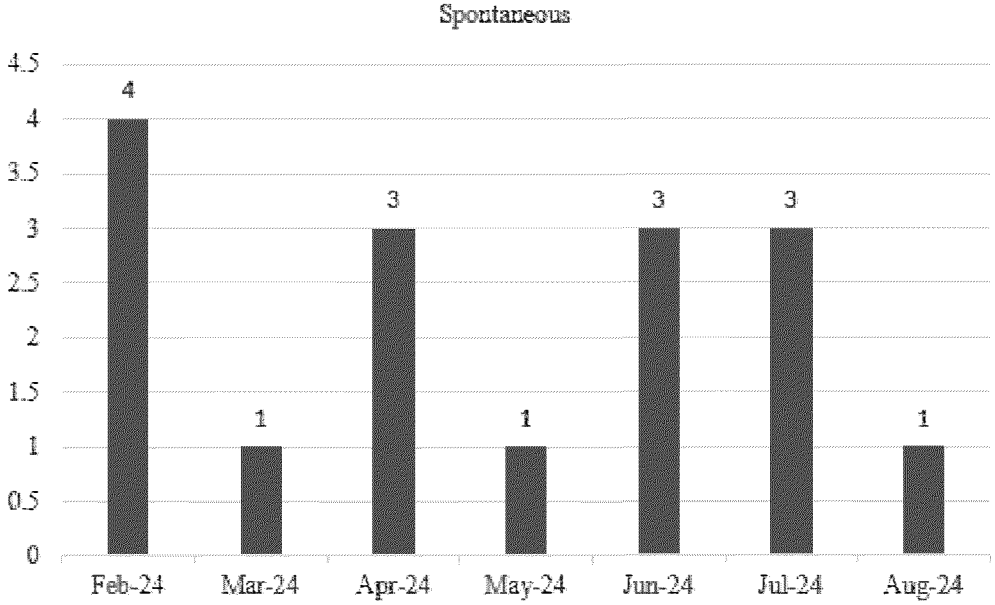
a: One case may report more than 1 event.

Of the total 17 cases reported as booster received during interval, 1 medically confirmed case reported a TTO >14 days and reported PTs consistent with a COVID-19 diagnosis or laboratory finding of positive PCR test confirming COVID-19 positivity. The event reported in this case is SARS-CoV-2 test positive.

No cases and events of suspected vaccination failure with booster doses were retrieved during the reporting interval.

Figure 2 depicts the monthly case count of spontaneous cases reported as booster from 25 February 2024 to 30 September 2024.

Figure 2: Case Count of Post-marketing Spontaneous Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Interval: 25 February 2024 to 30 September 2024).



The EOIs are further sorted by seriousness and their respective outcomes in Table 33 and Table 34.

Table 33: Serious MedDRA PTs and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=5)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events
Vaccination failure						2	2
COVID-19						1	1
Drug ineffective						1	1
Thrombosis with thrombocytopenia syndrome						1	1

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

Table 34: Nonserious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=28)

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Events
COVID-19 immunisation				12	12
COVID-19	1	1	3	3	8
Post-acute COVID-19 syndrome	2			1	3
SARS-CoV-2 test positive			2		2
Suspected COVID-19			1	1	2

Table 34: Nonserious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=28)

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Events
Breakthrough COVID-19				1	1

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

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.4.1 and Appendix 6.4.2, respectively.

Discussion

For the current reporting interval of 25 February 2024 to 30 September 2024, a total of 55 cases meeting the criteria for confirmed or suspected vaccination failure were reported, which is notably less than the number of cases identified for the previous PBRER interval of 25 February 2023 to 24 February 2023 (n=180). This decrease in number is due to the overall decrease in reporting of vaccination failure/lack of efficacy cases in the current reporting interval (total 274 cases) compared to the previous reporting interval (total of 682 cases) which in turn may be due to the lower exposure to the vaccine compared to last reporting interval.

In the current reporting interval, the country with the highest number of cases was Portugal, accounting for 87.9% of primary dose cases reported. Most of these cases were received in the month of March 2024 and April 2024. This spike resulted due to bulk reporting of cases by Health Authority, as all cases were received from Health authority (mostly EVHUMAN) with minimal case details ie, no medical history, concomitant medications and clinical course in the majority of cases, and not necessarily occurring within date of reporting to the Company. None of the reported events of interest in these cases were fatal, life-threatening or disabling; only 1 case reported hospitalisation.

There were 2 primary dose cases from the current interval that reported fatal outcome. Both of these cases were not assessed as confirmed LOE.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 16,924 vaccination failure case reports were received by the Company, of which 6,069 were

confirmed cases based on the WHO definition. No signals for vaccine failure were identified from post marketing experience during Ad26.COV2.S time in the market.

15.6. Reactogenicity

Introduction

Reactogenicity is a standard topic for review in vaccine PBRERs. Reactogenicity is the physical manifestation of inflammatory response(s) to vaccination. These responses may include injection site pain, redness, swelling, or induration at the injection site. In addition, systemic symptoms may be observed such as fever, myalgia, or headache. (Herve 2019)

Methods

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

Reported events were further sorted into local reactogenicity versus systemic reactogenicity reactions. Local reactogenicity reactions included HLT of Administration site reactions NEC, Injection site reactions, and Vaccination site reactions. Systemic reactogenicity reactions included MedDRA PTs of Headache, Pyrexia, Myalgia, Arthralgia, Vomiting, Diarrhoea, Paraesthesia, Hypoaesthesia, Dizziness, Chills, Fatigue, Asthenia, Muscular weakness, and Pain in extremity. Note: One case may have reported local as well as systemic reactogenicity EOI.

An additional manual review of the cases was performed with a maximum reported latency period of 1 week and only if leading to hospitalisation or considered life-threatening.

Results/Discussion

Primary Dose

During the reporting interval, a total of 3 medically unconfirmed primary dose cases reporting serious AEs of reactogenicity were identified. These 3 cases reported 3 serious EOI.

An overview of these cases is presented in Table 35.

Table 35: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=1,517
Sex	Male	3	682
	Female		818
	NR		17
Age (Years)[b]	0 to 17		4
Minimum: 23	18 to 35	1	460
Maximum: 69	36 to 50	1	493
Mean: 45.3	51 to 64		359
	≥65	1	172

Table 35: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=1,517
Median: 44	Adult		6
	NR		23
Source	Spontaneous	3	1,445
	Clinical Study (non-interventional, solicited)		57
	Clinical Trial		15
Country/Territory[c]	Germany	3	308
	US		478
	Korea, Republic of		105
	Romania		79
	South Africa		75
	Philippines		74
	Italy		55
	Netherlands		42
	Austria		36
	Greece		36
	Ireland		28
	Belgium		26
	Portugal		25
	Poland		21
Event Characteristics		**Number of Events=3**	**Number of Events=3,609**
Seriousness (Event Level)[d]	Serious	3	3,609
Outcome (Event Level)[d]	Not resolved	2	1,296
	Resolved with sequelae	1	114
	Resolving		754
	Resolved		723
	Fatal		70
	NR		652

Key: EOI=Event of Interest; NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative data.

b: The median and mean age calculations were based on the current reporting interval (25 February 2024 to 30 September 2024). Cases where the age was not reported, the age group has been presented.

c: The Country/Territory of origin with frequency ≥20 have been presented for cumulative data.

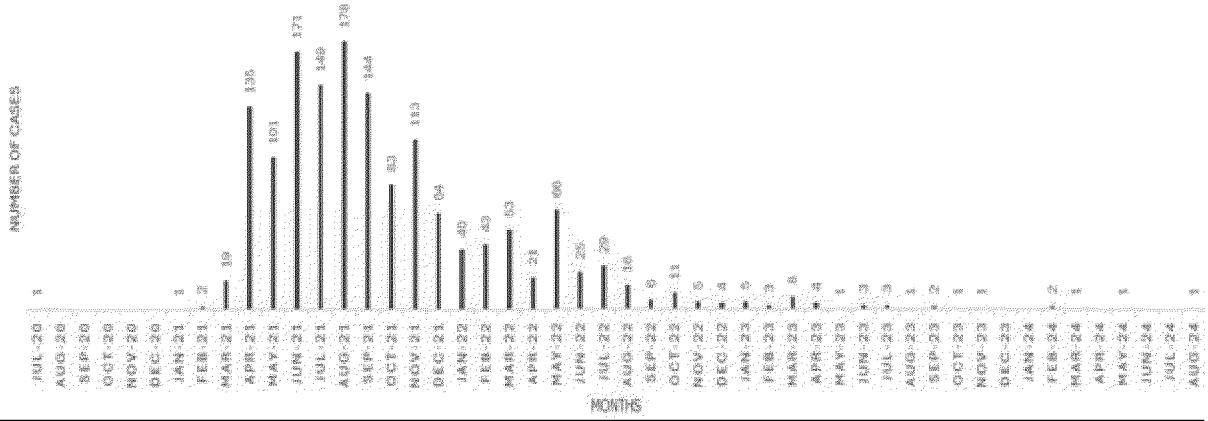
d: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

These 3 cases received during the reporting interval, were reported from Germany and concerned males. The age was reported in these 3 cases as 23, 44 and 69 years, respectively.

Cumulatively, 1,517 (688 medically confirmed and 829 medically unconfirmed) primary dose cases reporting reactogenicity were identified.

Figure 3 presents the number of cases received cumulatively by month (n=1,517).

Figure 3: Cumulative Case Reports by Month



Booster Dose

During the reporting interval, no initial cases reported as booster were identified.

Cumulatively, 47 (15 medically confirmed and 32 medically unconfirmed) cases reported as booster were identified.

Local Reactogenicity Reactions

Primary Dose

During the reporting interval, there were no initial primary dose cases reporting local reactogenicity reactions.

Cumulatively, 147 (51 medically confirmed and 96 medically unconfirmed) primary dose cases reported 244 local reactogenicity reactions. The frequency distribution of MedDRA PTs reflecting potential local reactions is presented in Table 36. The event outcomes are presented in Table 37.

Table 36: Frequency of MedDRA PTs of Interest in Primary Dose Cases Reporting Potential Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval	Number of Serious Events Received Cumulatively[a]
Injection site pain		129
Injection site swelling		30
Vaccination site pain		20
Injection site erythema		11
Administration site pain		8
Injection site reaction		5
Vaccination site reaction		4
Extensive swelling of vaccinated limb		3
Injection site bruising		3
Injection site induration		3
Injection site warmth		3

Table 36: Frequency of MedDRA PTs of Interest in Primary Dose Cases Reporting Potential Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval	Number of Serious Events Received Cumulatively[a]
Puncture site pain		3

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: MedDRA PTs of interest with frequency ≥3 have been presented for cumulative data.

Table 37: Frequency Distribution of MedDRA PTs of Interest and Outcomes in Primary Dose Cases Reporting Potential Local Reactogenicity Reactions Cumulatively With the Use of Ad26.CoV2.S

MedDRA PTs[a]	Number of Event Outcomes						
	Not Resolved	Resolving	Resolved	Resolved With Sequelae	Fatal	NR	Total Number of Serious Events
Injection site pain	37	42	30	1	1	18	129
Injection site swelling	5	7	10	0	0	8	30
Vaccination site pain	3	9	4	2	0	2	20
Injection site erythema	1	0	2	0	0	8	11
Administration site pain	1	2	2	1	1	1	8
Injection site reaction	1	1	1	1		1	5
Vaccination site reaction	2	0	0	0	0	2	4
Extensive swelling of vaccinated limb	0	0	2	0	0	1	3
Injection site bruising	0	1	1	0	0	1	3
Injection site induration	0	1	1	0	1	0	3
Injection site warmth	0	0	2	0	1	0	3
Puncture site pain	0	0	2	0	0	1	3
Total[b]	**61**	**63**	**64**	**5**	**5**	**46**	**244**

Key: MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term
a: MedDRA PTs of interest with frequency ≥3 have been presented.
b: Total count for outcome of the events of interest has been presented.

Cumulatively, the reported EOI with frequency (≥10) were injection site pain (n=129), injection site swelling (n=30), vaccination site pain (n=20), and injection site erythema (n=11). The mean and median TTO were 1 and 1 days, respectively, and the range was from 0 to 7 days. Of the 244 EOI, outcomes were reported for 198 and are as follows: resolved (n=64), resolving (n=63), not resolved (n=61), and fatal, resolved with sequelae (n=5, each).

Additionally, as no initial primary cases were retrieved during the reporting interval, there were no serious important identified risks (eg, TTS or thrombocytopenia, including immune thrombocytopenia) events reported.

Booster Dose

During the reporting interval, there were no booster cases reporting local reactogenicity reactions.

Cumulatively, 5 medically unconfirmed booster cases reported 6 local reactogenicity reactions. The frequency distribution of MedDRA PTs reflecting potential local reactions is presented in Table 38. The event outcomes are presented in Table 39.

Table 38: Frequency of MedDRA PTs of Interest in Booster Dose Cases Reporting Potential Local Reactogenicity Reactions Cumulatively With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval	Number of Serious Events Received Cumulatively
Injection site pain		2
Vaccination site pain		2
Injection site erythema		1
Injection site swelling		1

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

Table 39: Frequency Distribution of MedDRA PTs of Interest in Booster Dose Cases and Outcomes Reporting Potential Local Reactogenicity Reactions Cumulatively With the Use of Ad26.CoV2.S

MedDRA PTs	Number of Event Outcomes		
	Resolved	NR	Total Number of Serious Events
Injection site pain	2	0	2
Vaccination site pain	0	2	2
Injection site erythema	1	0	1
Injection site swelling	1	0	1
Grand Total	**4**	**2**	**6**

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

Cumulatively, the reported EOI were injection site pain, vaccination site pain (n=2, each), injection site erythema, and injection site swelling (n=1 each). The mean and median TTO were 0.3 and 0 days, respectively, and the range was from 0 to 1 days. Of the 6 EOI, outcomes were reported for 4 EOI as resolved (n=4).

Additionally, as no initial booster cases were retrieved during the reporting interval, there were no serious important identified risks (eg, TTS or thrombocytopenia, including immune thrombocytopenia) events reported.

Systemic Reactogenicity Reactions

Primary Dose

During the reporting interval, 3 primary dose cases reported 3 systemic reactogenicity reactions. All the cases reported were from [redacted] and concerned males. The age was reported in these 3 cases as 23, 44 and 69 years, respectively.

The reported EOI were asthenia, dizziness and headache (n=1 each). The mean and median TTO were 2.3 days and 0 day, respectively, and the range was from 0 to 7 days. Outcome was reported for all the 3 EOI, as not resolved (n=2) and resolved with sequelae (n=1).

Cumulatively, 1,489 (670 medically confirmed and 819 medically unconfirmed) primary dose cases reported 3,365 systemic reactogenicity reactions. The frequency distribution of MedDRA PTs reflecting potential systemic reactions is presented in Table 40. The events of interest outcomes are presented in Table 41.

Table 40: Frequency of MedDRA PTs of Interest in Primary Dose Cases Reporting Potential Systemic Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval[a]	Number of Serious Events Received Cumulatively
Headache	1	593
Pyrexia		430
Fatigue		384
Dizziness	1	383
Myalgia		249
Chills		245
Pain in extremity		170
Asthenia	1	160
Hypoaesthesia		158
Paraesthesia		156
Arthralgia		143
Vomiting		138
Diarrhoea		84
Muscular weakness		72

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

a: The MedDRA PTs of interest have been sorted by the decreasing order for the cumulative data. A single case may report more than 1 EOI.

Table 41: Frequency Distribution of MedDRA PTs of Interest and Outcomes in Primary Dose Cases Reporting Potential Systemic Reactogenicity Reactions Cumulatively With the Use of Ad26.CoV2.S

MedDRA PTs[a]	Number of Event Outcomes						
	Not Resolved	Resolved	Resolving	Resolved With Sequelae	Fatal	NR	Total Number of Serious Events
Headache	232	96	132	18	8	107	593
Pyrexia	84	146	97	14	16	73	430

Table 41: Frequency Distribution of MedDRA PTs of Interest and Outcomes in Primary Dose Cases Reporting Potential Systemic Reactogenicity Reactions Cumulatively With the Use of Ad26.CoV2.S

MedDRA PTs[a]	Number of Event Outcomes						
	Not Resolved	Resolved	Resolving	Resolved With Sequelae	Fatal	NR	Total Number of Serious Events
Fatigue	187	49	94	15	9	30	384
Dizziness	130	61	80	13	3	96	383
Myalgia	84	34	63	8	1	59	249
Chills	45	81	52	5	5	57	245
Pain in extremity	91	36	15	1		27	170
Asthenia	58	28	28	5	12	29	160
Hypoaesthesia	84	25	23	7		19	158
Paraesthesia	72	22	25	16		21	156
Arthralgia	66	14	35	3	3	22	143
Vomiting	30	43	24	3	4	34	138
Diarrhoea	28	16	16	1	4	19	84
Muscular weakness	44	8	7			13	72
Total	**1,235**	**659**	**691**	**109**	**65**	**606**	**3,365**

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

Cumulatively, the most frequently reported EOIs were headache (n=593), pyrexia (n=430), fatigue (n=384), and dizziness (n=383). The mean and median TTO were 1.5 and 1 days, respectively, and the range was from 0 to 7 days. Of the 3,365 EOI, outcomes were reported for 2,759 EOI and are as follows: not resolved (n=1,235), resolving (n=691), resolved (n=659), resolved with sequelae (n=109), and fatal (n=65).

Additionally, cases were reviewed to determine if there were any reported important identified risks (eg, TTS or thrombocytopenia, including immune thrombocytopenia). In these 3 cases, no important identified risk events were reported.

Booster Dose

During the reporting interval, there were no booster cases reporting systemic reactogenicity reactions.

Cumulatively, 47 (15 medically confirmed and 32 medically unconfirmed) booster cases reported 79 systemic reactogenicity reactions. The frequency distribution of MedDRA PTs reflecting potential systemic reactions is presented in Table 42. The events of interest outcomes are presented in Table 43.

Table 42: Frequency of MedDRA PTs of Interest in Booster Dose Cases Reporting Potential Systemic Reactogenicity Reactions Cumulatively With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval[a]	Number of Serious Events Received Cumulatively
Headache		17
Pyrexia		9
Fatigue		8
Pain in extremity		8
Dizziness		7
Hypoaesthesia		6
Paraesthesia		5
Arthralgia		4
Vomiting		4
Muscular weakness		3
Asthenia		2
Chills		2
Diarrhoea		2
Myalgia		2

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

a: The MedDRA PTs of interest have been sorted by the decreasing order for the cumulative data. A single case may report more than 1 EOI.

Table 43: Frequency Distribution of MedDRA PTs of Interest in Booster Dose Cases and Outcomes Reporting Potential Systemic Reactogenicity Reactions Cumulatively With the Use of Ad26.CoV2.S

MedDRA PTs	Number of Event Outcomes						
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	Fatal	NR	Total Number of Serious Events
Headache	6	4	1	1	1	4	17
Pyrexia	3	4	0	1	0	1	9
Fatigue	2	1	1	1	1	2	8
Pain in extremity	3	4	1	0	0	0	8
Dizziness	2		4	0	1	0	7
Hypoaesthesia	3	2	0	1	0	0	6
Paraesthesia	4	0	0	0	0	1	5
Arthralgia	1	1	1	1	0	0	4
Vomiting	2	0	0	1	0	1	4
Muscular weakness	1	1	1	0	0	0	3
Asthenia	1	1	0	0	0	0	2
Chills	0	1	0	1	0	0	2
Diarrhoea	2	0	0	0	0	0	2
Myalgia	0	1	1	0	0	0	2
Total	**30**	**20**	**10**	**7**	**3**	**9**	**79**

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

Cumulatively, the reported EOI with frequency (≥5) were headache (n=17); pyrexia (n=9); fatigue, pain in extremity (n=8 each); dizziness (n=7); hypoaesthesia (n=6); and paraesthesia (n=5). The mean and median TTO were 1.8 days, and 1 day, respectively, and the range was from 0 to 7 days. Of the 79 EOI, outcomes were reported for 70 and are as follows: not resolved (n=30),

resolved (n=20), resolved with sequelae (n=10), resolving (n=7), and fatal (n=3).

Additionally, as no initial booster cases were retrieved during the reporting interval, there were no serious important identified risks (eg, TTS or Thrombocytopenia, including immune thrombocytopenia) events reported.

Literature ICSR

No ICSR literature cases were received during the reporting interval.

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.5.1 and Appendix 6.5.2 respectively

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 1,564 case reports of reactogenicity have been received by the Company. The reported local and systemic reactions received during the reporting period are in line with what is already included in the product information as common adverse reactions. The review of the cases received during the reporting interval have not shown any changes in terms of severity or outcome warranting changes to the prescribing information (PI).

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

16.1.1. At the Beginning of the Reporting Interval

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting interval to be included in the Ad26.COV2.S PBRER is based on the cRMP (version 8.0, dated 06 February 2024) and is summarised in Table 44.

In addition, the summary of safety concerns is also based on the following:

- Important risk and missing information definitions provided in the ICH E2C guidelines on the PBRER and GVP Module VII - Periodic Safety Update Report
- Any additional safety concerns per other regional or country/territory-specific RMP requirements, as applicable.
- European Union (EU) RMP: version 7.1 (dated 13 June 2023).
- European Medicines Agency (EMA) core PSUR 19 guidance (EMA/362988/2021 dated 08 July 2021).

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

Table 44: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Interval

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

Key: EU=European Union; RMP=Risk Management Plan; VAERD=Vaccine-associated enhanced respiratory disease

a: This topic is included in the EU RMP only.

16.1.2. At the End of the Reporting Interval

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

The EU RMP version 7.1 (dated 13 June 2023) was updated to version 8.2 (dated 12 July 2024) with the removal of the missing information "Interaction with other vaccines".

The EU RMP version 8.2 (dated 12 July 2024) was further updated to version 8.3[15] (dated 04 June 2024) and submitted on 28 June 2024 under Type II variation Procedure No. EMEA/H/C/005737/II/0078/G to EMA, however before the completion of the procedure the marketing authorisation was withdrawn. These updates are discussed under appropriate subsections below including Section 16.3, Evaluation of Risks and New Information

The updated summary of safety concerns is presented in Table 45.

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

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Venous thromboembolism Myocarditis and pericarditis Thrombocytopenia, including immune thrombocytopenia
Important Potential Risks	Vaccine-associated enhanced disease, including VAERD
Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders

15 The EU RMP version 8.3 is not formally approved by EMA.

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

	Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
	Long-term safety

Key: EU=European Union; RMP=Risk Management Plan; VAERD=Vaccine-associated enhanced respiratory disease

16.2. Signal Evaluation

16.2.1. Closed Signals

This section presents those signals which were closed within the STS, following the PBRER ICH E2C guidelines and Module VII of the GVP. This represents that the evaluation and review process has been completed. Depending on the outcome of the evaluation, these signals may continue to be monitored by regular pharmacovigilance (PV) activities or closely monitored and discussed in future PBRERs/PSURs.

16.2.1.1. Closed and Refuted Signals

During the reporting interval, there were no closed signals that were refuted.

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

No closed signals were categorised as important potential risks.

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

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

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

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

16.3. Evaluation of Risks and New Information

In accordance with GVP Module VII, the Company collectively assesses new information received during the reporting interval from ICSRs (initial and follow-up), clinical studies (if applicable), registries (if applicable), and the literature to determine if the new information changes the characterisation of these risks.

16.3.1. New Information on Important Identified Risks

16.3.1.1. Thrombosis With Thrombocytopenia Syndrome

Introduction

According to the cRMP (version 8.0; dated 06 February 2024) and EU RMP (version 7.1, dated 13 June 2023), thrombosis with thrombocytopenia syndrome (TTS) is an important identified risk associated with the use of Ad26.COV2.S Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

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

Results/Discussion

Primary Dose

During this reporting interval, a total of 8 medically confirmed initial, primary dose cases reporting TTS were retrieved. These serious cases reported a total of 8 serious EOI.

Cumulatively, 387 (311 medically confirmed and 76 medically unconfirmed) primary dose cases reporting TTS were retrieved. There were 385 serious and 2 nonserious cases which reported a total of 1,292 EOI (1267 serious, 25 nonserious). A single case may report more than 1 EOI.

An overview of these cases is presented in Table 46.

Table 46: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=8[a]	Number of Cases Received Cumulatively=387
Sex	Female	2	178
	Male	2	172
	NR	4	37
Age (Years)[b]	18 to 35	1	72
Minimum: 29	36 to 50	1	117
Maximum: 78	51 to 64	1	103
Mean: 52.5	≥65	1	53
Median: 51.5	Adult		5
	NR	4	37
Source	Spontaneous	5[c]	345
	Clinical Study (non-interventional, solicited)	3[c]	22
	Clinical Trial		19
	Clinical Study		1

Table 46: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=8[a]	Number of Cases Received Cumulatively=387
	(non-interventional, unsolicited)		
Country/Territory[d]	US	2	211
	Germany	1	52
	Italy	1	16
	Netherlands	3	16
	Spain		15
	Brazil		9
	Greece		9
	Poland		9
	South Africa		8
	France		7
	Slovenia		6
	Canada	1	5
Event Characteristics		**Number of EOI=8**	**Number of EOI=1,292**
Seriousness (Event Level)[e]	Serious	8	1,267
	Nonserious		25
Outcome (Event Level)[e]	Not resolved		403
	Fatal		186
	Resolved	1	135
	Resolving		132
	Resolved with sequelae		19
	NR	7	417

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). For cases where age was not reported, age group has been presented.

c: This count included all cases from literature sources (5 spontaneous and 3 clinical study [non-interventional, solicited] sources).

d: Countries with frequency of≥5 cumulatively have been presented.

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

Of these 8 initial, primary dose cases received, the most frequently reported countries/territories of origin were Netherlands (n=3) and the US (n=2). These cases concerned 2 males, 2 females, and 4 cases did not report sex. The age range was from 29 to 78 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 47.

Table 47: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia			191	11
Thrombosis with thrombocytopenia syndrome	8		117	
Pulmonary embolism			104	
Platelet count decreased			103	10
Thrombosis			78	
Cerebral venous sinus thrombosis			76	
Deep vein thrombosis			76	
Portal vein thrombosis			25	
Cerebrovascular accident			24	
Immune thrombocytopenia			24	
Disseminated intravascular coagulation			20	
Ultrasound Doppler abnormal			16	2
Jugular vein thrombosis			16	
Thrombotic thrombocytopenic purpura			16	
Acute myocardial infarction			15	
Cerebral venous thrombosis			15	
Superior sagittal sinus thrombosis			15	
Transverse sinus thrombosis			15	
Hemiparesis			11	
Venogram abnormal			11	
Cerebral infarction			10	
Cerebral thrombosis			10	
Venous thrombosis			10	
Angiogram cerebral abnormal			9	
Peripheral artery thrombosis			9	
Thrombectomy			9	
Haemorrhagic stroke			8	
Hepatic vein thrombosis			8	
Myocardial infarction			8	
Transient ischaemic attack			8	
Visceral venous thrombosis			8	
Aortic thrombosis			7	
Pulmonary thrombosis			7	
Renal infarct			7	
Splenic infarction			7	
Splenic vein thrombosis			7	
Superficial vein thrombosis			6	1
Carotid artery thrombosis			6	
Embolism			6	
Mesenteric vein thrombosis			6	
Portosplenomesenteric venous thrombosis			6	
Arterial thrombosis			5	
Hemiplegia			5	
Renal vein thrombosis			5	
Sigmoid sinus thrombosis			5	

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

Table 47: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: The MedDRA PTs of interest were sorted by decreasing order for the cumulative; The events with frequency ≥5 were presented.

The EOI reported in all these 8 cases received in the reporting interval was Thrombosis with thrombocytopenia syndrome (n=8). The Time to Onset (TTO) was not reported in all the 8 cases. Where reported (n=1), outcome was reported as resolved.

Of these 387 primary dose cases received cumulatively, the Company identified 344 primary dose cases that met case definition for TTS and are stratified by age group and sex and for Brighton Collaboration (BC), Centers for Disease Control (CDC), and Pharmacovigilance Risk Assessment Committee (PRAC) criteria (see Table 48).

Table 48: Number of Primary Dose Cases by Age and Sex and Working Case Definitions for Cases Reporting Thrombosis With Thrombocytopenia syndrome With the Use of Ad26. COV2.S Vaccine Cumulatively (Number of Cases=344; Number of Events of Interest=1,193)

Age Group (Years)	18 to 35			36 to 50			51 to 64			≥65			Adult			NR		
Sex	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**
CDC																		
Tier 1	13	15	3	36	10	2	12	10	0	7	2	0	0	0	0	0	0	0
Tier 2	1	6	0	2	4	0	4	4	0	0	0	0	0	0	0	0	0	0
Neither	12	16	0	24	33	1	28	36	1	20	21	0	3	0	2	3	2	11
Total	**26**	**37**	**3**	**62**	**47**	**3**	**44**	**50**	**1**	**27**	**23**	**0**	**3**	**0**	**2**	**3**	**2**	**11**
Brighton Collaboration																		
Level 1	15	20	2	36	20	0	26	25	0	10	7	0	1	0	0	1	0	0
Level 2	1	1	0	2	0	0	0	0	0	1	1	0	0	0	0	0	0	0
Level 3	1	2	1	4	1	2	1	3	0	1	2	0	0	0	0	0	0	0
Level 4	9	13	0	16	25	1	15	15	1	10	9	0	2	0	2	2	2	11
Level 5	0	1	0	4	1	0	2	7	0	5	4	0	0	0	0	0	0	0
Total	**26**	**37**	**3**	**62**	**47**	**3**	**44**	**50**	**1**	**27**	**23**	**0**	**3**	**0**	**2**	**3**	**2**	**11**
PRAC																		
Confirmed	6	8	2	16	4	1	2	2	0	0	1	0	0	0	0	0	0	0
Probable	1	2	1	6	2	0	2	2	0	0	1	0	0	0	0	0	0	1
Possible	17	23	0	34	37	2	36	35	0	22	14	0	2	0	1	3	2	8
Unlikely	0	0	0	2	1	0	2	3	0	2	2	0	0	0	0	0	0	0
Criteria not met	2	4	0	4	3	0	2	8	1	3	5	0	1	0	1	0	0	2
Total	**26**	**37**	**3**	**62**	**47**	**3**	**44**	**50**	**1**	**27**	**23**	**0**	**3**	**0**	**2**	**3**	**2**	**11**

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

Booster Dose

During this reporting interval, 1 medically confirmed initial, booster dose serious case reporting TTS was retrieved and reported 1 serious EOI. This case was heterologous.

Cumulatively, 10 (9 medically confirmed and 1 medically unconfirmed) booster dose cases reporting TTS were retrieved. These 10 serious cases reported a total of 32 serious EOI. All of these 10 cases were heterologous. A single case may report more than 1 EOI.

An overview of these cases is presented in Table 49.

Table 49: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=1[a]	Number of Cases Received Cumulatively=10
Sex	Male		5
	Female		2
	NR	1	3
Age (Years)	18 to 35		3
Minimum: NA	36 to 50		3
Maximum: NA	51 to 64		1
Mean: NA	≥65		1
Median: NA	NR	1	2
Source	Spontaneous	1[b]	5
	Clinical study (non-interventional, solicited)		5
Country/Territory	Germany		6
	Brazil		1
	Greece		1
	Italy	1	1
	US		1
Classification	Heterologous	1	10
	Homologous		
Event Characteristics		**Number of EOI=1**	**Number of EOI=32**
Seriousness (Event Level)[c]	Serious	1	32
	Nonserious		
Outcome (Event Level)[c]	Not resolved		8
	Fatal		6
	Resolved		5
	NR	1	13

Key: EOI=Event(s) of Interest; NA=Not Available; NR=Not Reported; US=United States
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: This count included the case from literature source.
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

This 1 case reported during the reporting interval, as booster was from the country/territory of origin Italy. This case did not report the sex and age of the patient.

The frequency distribution of the MedDRA PTs of interest reported in booster dose cases is presented in Table 50.

Table 50: Frequency Distribution of MedDRA PTs of Interest in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	1		8	
Cerebral venous sinus thrombosis			4	
Deep vein thrombosis			3	
Cerebrovascular accident			2	
Pulmonary embolism			2	
Angiogram cerebral abnormal			1	
Aortic thrombosis			1	
Cerebral venous thrombosis			1	
Coronary artery thrombosis			1	
Immune thrombocytopenia			1	
Jugular vein thrombosis			1	
Myocardial infarction			1	
Pelvic venous thrombosis			1	
Platelet count decreased			1	
Thrombocytopenia			1	
Thrombotic thrombocytopenic purpura			1	
Vena cava thrombosis			1	
Venous thrombosis			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: The MedDRA PTs of interest were sorted by decreasing order for the cumulative..

The EOI reported during the reporting interval was Thrombosis with thrombocytopenia syndrome (n=1). The TTO and the outcome was not reported.

Of these 10 booster dose cases received cumulatively, the Company identified 9 booster dose cases that met case definition for TTS and are stratified by age group and sex and for BC, Centers for Disease Control (CDC), and Pharmacovigilance Risk Assessment Committee (PRAC) criteria (see Table 51).

Table 51: Number of Booster Cases by Age and Sex and Working Case Definitions for Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26. COV2.S Vaccine Cumulatively (Number of Cases=9; Number of Events of Interest=31)

Age Group(Years)	18 to 35			36 to 50			51 to 64			≥65			NR		
Sex	F	M	NR	F	M	NR	F	M	NR	F	M	NR	F	M	NR
CDC															
Tier 1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Tier 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 51: Number of Booster Cases by Age and Sex and Working Case Definitions for Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26. COV2.S Vaccine Cumulatively (Number of Cases=9; Number of Events of Interest=31)

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

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

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.6.1 and Appendix 6.6.2.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 353 case reports meeting the definition of TTS have been received by the Company, of which 60 had a fatal outcome. The data received during the reporting period is consistent with the characterization of this risk, and no further safety measures are deemed necessary.

16.3.1.2. Guillain-Barré Syndrome

Introduction

According to the cRMP (version 8.0; dated 06 February 2024), Guillain-Barré Syndrome (GBS) is an important identified risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

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

Results/Discussion

Primary Dose

During this reporting interval, a total of 12 (6 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting GBS were retrieved. One case was not further discussed since it involved multiple patients with no patient identifiers. The remaining 11 cases (5 medically confirmed and 6 medically unconfirmed), all of which were assessed as serious, reported a total of 12 serious EOI.

Cumulatively, 679 (388 medically confirmed and 291 medically unconfirmed) primary dose cases reporting GBS were retrieved. Twenty-one cases were not further discussed since these involved multiple patients with no patient identifiers. The remaining 658 cases (369 medically confirmed and 289 medically unconfirmed) were all assessed as serious which reported a total of 696[16] serious EOI.

An overview of these cases is presented in Table 52.

Table 52: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=11[a]	Number of Cases Received Cumulatively=658
Sex	Male	7	399
	Female	3	238
	NR	1	21
Age (Years)[b]	18 to 35	2	77
Minimum: 20	36 to 50	1	185
Maximum: 64	51 to 64	3	254
Mean: 45.5	≥65		89
Median: 48.5	Adult		4
	Elderly		1
	NR	5	48
Sources	Spontaneous	11	646
	Clinical Trial		12
Country/Territory[c]	US	3	338
	Germany	2	89

[16] In case [redacted] Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) is coded thrice. All 3 events of CIDP have been reported with the same onset date and based on the reported case comments, there has been 1 occurrence of the event.Therefore, only 1 CIDP is included in the counts.

Table 52: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=11[a]	Number of Cases Received Cumulatively=658
	Spain		26
	France		21
	Italy		21
	Korea, Republic of		21
	Netherlands		20
	South Africa	1	19
	Brazil		14
	Portugal		12
	Philippines	1	9
	Poland	1	8
	Belgium		7
	Greece		7
	Ireland		7
	Colombia		5
	Mexico		5
	Austria		4
	Egypt	2	4
	Latvia		4
	Luxembourg		2
	Peru		2
	Switzerland	1	2
Event Characteristics		**Number of Events=12**	**Number of Events=696**
Seriousness (Event Level)[d]	Serious	12	696[e]
Outcome (Event Level)[d]	Not resolved	4	331
	Resolving	3	133
	Resolved		38
	Resolved with sequelae		35
	Fatal		7
	NR	5	154

Key: CIDP= Chronic Inflammatory Demyelinating Polyradiculoneuropathy; EOI=Event of Interest; NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). Age group was presented for cases where age was not reported.

c: Countries/territories with frequency ≥2 were presented in decreasing order based on the cumulative counts.

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

e: In case [redacted] Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is coded thrice. All 3 events of CIDP have been reported with the same onset date and based on the reported case comments, there has been 1 occurrence of the event. Therefore, only 1 CIDP event is included in the counts.

Of the 11 primary dose cases received, the most frequently reported countries/territories of origin (n≥2) were the US (n=3), and Egypt and Germany (n=2 each). These cases concerned 7 males, 3 females, and 1 case did not report sex. Where reported (n=6), the age range was from 20 to 64 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 53.

Table 53: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Guillain-Barré Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	10		590	
Chronic inflammatory demyelinating polyradiculoneuropathy	2		56[b]	
Demyelinating polyneuropathy			19	
Miller Fisher syndrome			16	
Subacute inflammatory demyelinating polyneuropathy			8	
Acute motor axonal neuropathy			2	
Acute motor-sensory axonal neuropathy			2	
Bickerstaff's encephalitis			2	
Ascending flaccid paralysis			1	

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

a: For the interval (25 February 2024 to 30 September 2024) column, the EOI were presented in decreasing order based on the cumulative counts. A single case may report more than 1 MedDRA PT.

b: In case [redacted] Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) is coded thrice. All 3 events of CIDP have been reported with the same onset date and based on the reported case comments, there has been 1 occurrence of the event. Therefore, only 1 CIDP event is included in the counts.

During the reporting interval, the EOI included Guillain-Barré syndrome (n=10) and chronic inflammatory demyelinating polyradiculoneuropathy (n=2). The mean and median TTO were 203.3 and 113 days, respectively, and the range was from 17 to 480 days. Where reported (n=7), the outcomes of the EOI were reported as follows: not resolved (n=4) and resolving (n=3).

Booster Dose

During this reporting interval, no initial case reported as booster was identified.

Cumulatively, 20 (7 medically confirmed and 13 medically unconfirmed) cases reported as booster were identified. Of these cases, there were 19 serious and 1 nonserious case which reported a total of 20 EOI (19 serious; 1 nonserious). Of these 20 cases, 11 were heterologous and 9 were homologous.

An overview of these cases is presented in Table 54.

Table 54: Characteristics of Booster Dose Cases Involving the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=0	Number of Cases Received Cumulatively=20
Sex	Male		11
	Female		8
	NR		1
Age (Years)[a]	18 to 35		2
Minimum: NA	36 to 50		2
Maximum: NA	51 to 64		6
Mean: NA	≥65		7
Median: NA	Adult		
	Elderly		
	NR		3
Sources	Spontaneous		19
	Clinical Trial		1
Country/Territory	Brazil		4
	Germany		4
	US		4
	Philippines		2
	Portugal		2
	South Africa		2
	Egypt		1
	Netherlands		1
Classification	Heterologous		11
	Homologous		9
Event Characteristics		**Number of Events=0**	**Number of Events=20**
Seriousness (Event Level)[b]	Serious		19
	Nonserious		1
Outcome (Event Level)[b]	Resolving		5
	Not resolved		4
	Fatal		2
	Resolved		1
	Resolved with sequelae		1
	NR		7

Key: NA=Not Applicable; NR=Not Reported; US=United States

a: During the current reporting interval (25 February 2024 to 30 September 2024), no initial case reported as booster was identified, hence median and mean age are not applicable.

b: 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 is presented in Table 55.

Table 55: Frequency Distribution of MedDRA PTs of Interest in Booster Dose Cases Reporting Guillain-Barré Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome			15	
Chronic inflammatory demyelinating polyradiculoneuropathy			1	1
Demyelinating polyneuropathy			2	
Miller Fisher syndrome			1	

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

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.7.1 and Appendix 6.7.2 respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 678 case reports of GBS have been received by the Company, of which 15 had a fatal outcome. The data received during the reporting period is consistent with the characterization of this risk, and no further safety measures are deemed necessary. .

16.3.1.3. Venous Thromboembolism

Introduction

According to the cRMP (version 8.0, dated 06 February 2024), Venous Thromboembolism (VTE) is an important identified risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

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

Results/Discussion

Primary Dose

During this reporting interval, a total of 11 serious (2 medically confirmed and 9 medically unconfirmed) primary dose cases reporting VTE were retrieved. All these cases were serious and reported a total of 14 EOI (13 serious; 1 nonserious).

Cumulatively, 2,493 (1,764 medically confirmed and 729 medically unconfirmed) primary dose cases reporting VTE were retrieved. There were 2,355 serious and 138 nonserious cases, which reported a total of 3,182 EOI (2,994 serious, 188 nonserious).

An overview of these cases is presented in Table 56.

Table 56: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Interval=11[a]	Number of Cases Received Cumulatively=2,493
Sex	Male	8	1,256
	Female		1,160
	NR	3	77
Age (Years)[b]	0-17		2
Minimum: 18			
Maximum: 66	18 to 35	1	307
Mean: 44.7	36 to 50	2	646
Median: 46	51 to 64	2	818
	≥65	1	570
	Adult	1	19
	Elderly		2
	NR	4	130
Source	Spontaneous	9[c]	2,235
	Clinical study (interventional unsolicited)		227
	Clinical study (non-interventional, solicited)	2	31
Country/Territory[d]	US	4	1,664
	Germany	2	235
	Netherlands	2	81
	France		78
	South Africa		66
	Spain		55
	Italy	2	54
	Brazil		37
	Poland	1	37
	Belgium		25
	Greece		19
	Austria		16
	Portugal		16
	Argentina		13
	Ireland		10

Table 56: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Interval=11[a]	Number of Cases Received Cumulatively=2,493
Event Characteristics		**Number of Events=14**	**Number of Events=3,182**
Seriousness (Event Level)[c]	Serious	13	2,994
	Nonserious	1	188
Outcome (Event Level)[c]	Not resolved	3	1,262
	Resolved	3	524
	Resolving	1	365
	Fatal		190
	Resolved with sequelae		38
	NR	7	803

Key: NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in the decreasing order based on the cumulative period (till 30 September 2024).

b: The median, mean age calculation, minimum, and maximum age value were based on the current reporting interval (25 February 2024 to 30 September 2024). The age group was presented for cases where age was not reported.

c: The count includes 1 literature case.

d: The country counts with frequency ≥10 were presented in decreasing order based on the cumulative period count (till 30 September 2024).

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

Of these 11 primary dose cases received during the reporting interval, the most frequently reported countries/territories of origin were the US (n=4), Germany, Italy and Netherlands (n=2 each), followed by Poland (n=1). Eight of these 11 cases concerned males, and 3 did not report sex. The age range was from 18 to 66 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 57.

Table 57: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Venous Thromboembolism With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	**Nonserious**	**Serious**	**Nonserious**
Pulmonary embolism	6		1,094	11
Deep vein thrombosis	4		886	40
Pulmonary thrombosis			196	
Cerebral venous sinus thrombosis	2		157	
Superficial vein			47	61

Table 57: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Venous Thromboembolism With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
thrombosis				
Thrombophlebitis			29	32
Venous thrombosis		1	42	14
Portal vein thrombosis	1		55	
Venous thrombosis limb			43	10
Cerebral venous thrombosis			40	
Pulmonary infarction			32	
Renal vein occlusion			28	2

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the interval (25 February 2024 to 30 September 2024) column, the events were presented in decreasing order based on the event counts of the cumulative.
b: The MedDRA PTs of interest were sorted by the decreasing order for the cumulative. The events reported with frequency ≥30 were presented A single case may report more than 1 MedDRA PT of interest.

During the reporting interval, the most common EOI reported was pulmonary embolism (n=6), followed by deep vein thrombosis (n=4). The mean and median TTO were 759.2 and 646.5 days, respectively, and the range was from 59 to 1375 days. Of the 14 EOI, outcomes were reported for 7 and are as follows: not resolved, resolved (n=3 each), and resolving (n=1).

Booster Dose

During this reporting interval, a total of 4 (2 medically confirmed and 2 medically unconfirmed) initial cases reported as booster were retrieved. All 4 cases were serious and reported a total of 4 EOIs (all serious). All 4 cases were homologous.

Cumulatively, a total of 113 (77 medically confirmed and 36 medically unconfirmed) cases reported as booster were identified. Of the 113 cases, 96 were serious and 17 were nonserious. These 113 cases reported a total of 138 EOI (119 serious; 19 nonserious). Of these cases, 86 were homologous and 27 were heterologous.

An overview of these cases is presented in Table 58.

Table 58: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Interval=4[a]	Number of Cases Received Cumulatively=113
Sex	Male	2	67
	Female	2	43
	NR		3

Table 58: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Interval=4[a]	Number of Cases Received Cumulatively=113
Age (Years)[b] **Minimum: 23** **Maximum: 60** **Mean: 38.5** **Median: 35.5**	0 to 17		1
	18 to 35	2	10
	36 to 50	1	32
	51 to 64	1	28
	≥65		35
	NR		7
Source	Spontaneous	4[c]	89
	Clinical source (interventional non solicited)		20
	Clinical source (non-interventional solicited)		3
	Clinical source (non-interventional unsolicited)		1
Country/Territory[d]	US	1	62
	Brazil		13
	Germany	1	12
	Belgium		5
	South Africa		5
	United Kingdom		4
	Austria		2
	France		2
	Italy	1	1
	Netherlands	1	1
Classification	Homologous	4	86
	Heterologous		27
Event Characteristics		**Number of Events=4**	**Number of Events=138**
Seriousness (Event Level)[c]	Serious	4	119
	Nonserious		19
Outcome (Event Level)[c]	Not Resolved	2	31
	Resolved		31
	Resolving		19
	Fatal		4
	Resolved with sequelae	1	4
	NR	1	49

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in the decreasing order based on the cumulative period (till 30 September 2024).

Table 58: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics	Number of Cases Received During the Reporting Interval=4[a]	Number of Cases Received Cumulatively=113

b: The median and mean age calculations were based on the current reporting interval (25 February 2024 to 30 September 2024).
c: The count also includes 1 literature case.
d: For the cumulative count, the counts were presented in the decreasing order.
e: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 4 cases reported as booster during the reporting interval, the countries/territories of origin reported were Germany, Italy, Netherlands, and the US (n=1 each). These cases concerned 2 males and 2 females. The age range was from 23 to 60 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 59.

Table 59: Frequency Distribution of MedDRA PTs of Interest in Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively[a]	
MedDRA PTs	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	1		42	9
Pulmonary embolism	2		36	1
Pulmonary thrombosis			10	
Cerebral venous sinus thrombosis	1		5	
Superficial vein thrombosis			1	4
Central venous catheterisation			3	
Pulmonary infarction			3	
Venous thrombosis limb				3
Jugular vein thrombosis			2	
Mesenteric vein thrombosis			2	
Pelvic venous thrombosis			2	
Retinal vein occlusion			2	
Retinal vein thrombosis			2	
Thrombophlebitis			1	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with frequency ≥2 are sorted and presented by decreasing order for the cumulative period (till 30 September 2024). A single case may report more than 1 MedDRA PT of interest.

During the reporting interval, the EOI included pulmonary embolism (n=2); deep vein thrombosis, and cerebral venous sinus thrombosis (n=1 each). Both mean and median for TTO were 615.5 days and the range was from 331 to 900 days. Of the 4 EOI, outcomes were reported for 3 EOI and are as follows: not resolved (n=2) and resolved with sequelae (n=1).

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary, and booster is presented in Appendix 6.8.1 and Appendix 6.8.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 2,606 case reports of VTE have been received by the Company, of which 183 had a fatal outcome. The data received during the reporting period is consistent with the characterization of this risk, and no further safety measures are deemed necessary. .

16.3.1.4. Myocarditis and pericarditis

Introduction

The cRMP (version 8.0, dated 06 February 2024) and EU RMP (version 7.1, dated 13 June 2023) includes myocarditis and pericarditis as an important identified risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

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

Results/Discussion

Primary Dose

During this reporting interval, a total of 13 (4 medically confirmed and 9 medically unconfirmed) initial, primary dose cases reporting myocarditis and pericarditis were retrieved. All these serious cases reported 14 serious EOI.

Cumulatively, 481 (277 medically confirmed and 204 medically unconfirmed) primary dose cases reporting myocarditis and pericarditis were retrieved. All cases were serious and reported a total of 505 serious EOIs. A single case may report more than 1 EOI.

An overview of these cases is presented in Table 60.

Table 60: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Interval=13[a]	Number of Cases Received Cumulatively=481
Sex	Male	5	304
	Female	5	142
	NR	3	35
Age (Years)[b]	18 to 35	2	190
Minimum: 22	36 to 50	5	101
Maximum: 50	51 to 64		107
Mean: 38.4	≥65		32
Median: 41	Child		1
	Adult	1	7
	NR	5	43
Sources	Spontaneous	11[c]	464
	Clinical Trial		10
	Clinical Study (non-interventional, solicited)	2[c]	7
Country/Territory[d]	US	2	217
	Germany	1	83
	Netherlands		31
	Italy	2	17
	France		14
	Austria		13
	Greece		11
	South Africa		11
	Denmark		10
	Belgium	1	9
	Portugal	1	8
	Brazil	2	7
	Spain		7
	Ireland		5
	Poland		5
Event Characteristics		**Number of Events=14**	**Number of Events=505**
Seriousness (Event Level)[e]	Serious	14	505
Outcome (Event Level)[e]	Not resolved	3	169
	Resolved	1	79
	Resolving	2	70
	Fatal	1	20
	Resolved with sequelae		17
	NR	7	150

Table 60: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics	Number of Cases Received During the Reporting Interval=13[a]	Number of Cases Received Cumulatively=481

Key: EOI=Event(s) of Interest; NR=Not Reported; US=United States
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). Cases where age was not reported, age group has been presented.
c: This count included 3 cases from literature sources (1 spontaneous and 2 solicited sources).
d: Countries with frequency of ≥5 cumulatively have been presented.
e: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

In these 13 initial, primary dose cases received, the most frequently reported countries/territories of origin were Brazil, Italy and the US (n=2 each). These cases concerned 5 females, 5 males, and 3 cases that did not report sex. The age range was from 22 to 50 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 61.

Table 61: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Myocarditis and Pericarditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	10		249	
Pericarditis	4		213	
Myopericarditis			35	
Pleuropericarditis			4	
Autoimmune myocarditis			1	
Eosinophilic myocarditis			1	
Giant cell myocarditis			1	
Pericarditis constrictive			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

The EOI reported during the reporting interval included myocarditis (n=10) and pericarditis (n=4). The mean and median TTO were 543.2 and 714 days, respectively, and the range was from 0 to 805 days. Where reported (n=7), the outcome for the EOI were as follows: not resolved (n=3), resolving (n=2), fatal (n=1), and resolved (n=1).

Booster Dose

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

interest. All 3 cases were homologous.

Cumulatively, 45 (19 medically confirmed and 26 medically unconfirmed) cases reported as booster were retrieved. All these serious cases reported 51 serious EOI. Of these cases, 22 were heterologous and 23 were homologous. A single case may report more than 1 EOI.

An overview of these cases is presented in Table 62.

Table 62: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=45
Sex	Male	2	30
	Female	1	10
	NR		5
Age (Years)[b]	18 to 35	1	16
Minimum: 19	36 to 50	1	13
Maximum:49	51 to 64		5
Mean: 34	≥65		3
Median: 34	Adult		2
	NR	1	6
Sources	Spontaneous	3[c]	41
	Clinical Study (non-interventional, solicited)		3
	Clinical Trial		1
Country/Territory	US	1	11
	Germany		10
	Iceland		5
	Austria		4
	South Africa		4
	Belgium		3
	Greece		2
	Lithuania	2	2
	Croatia		1
	Hungary		1
	Italy		1
	Portugal		1
Classification	Homologous	3	23
	Heterologous	0	22
Event Characteristics		**Number of Events of Interest=4**	**Number of Events of Interest=51**
Seriousness (Event Level)[d]	Serious	4	51
Outcome (Event Level)[d]	Not resolved		9
	Resolved	1	8
	Resolving	1	6

Table 62: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=45
	Resolved with sequelae		2
	NR	2	26

Key: EOI=Event(s) of Interest; NR=Not Reported; US=United States
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: The median and mean age calculations were based on the current reporting interval (25 February 2024 to 30 September 2024). For cases where age was not reported, age group has been presented.
c: This count included 2 cases from literature sources.
d: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

In these 3 cases reported as booster, the reported countries/territories of origin were Lithuania (n=2), followed by the US (n=1). These cases concerned 2 males, and 1 female. Where reported (n=2), the age was 19 years and 49 years.

The frequency distribution of the MedDRA PTs of interest reported in cases reported as booster is presented in Table 63.

Table 63: Frequency Distribution of MedDRA PTs of Interest in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	3		31	
Pericarditis	1		19	
Myopericarditis			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

The EOI reported during the reporting interval were myocarditis (n=3) and pericarditis (n=1). The mean and median TTO was 0 (same day). Where reported (n=2), the outcome for the EOI were as follows: resolved (n=1) and resolving (n=1).

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.9.1 and Appendix 6.9.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 526 case reports of myocarditis and pericarditis have been received by the Company, of which 24 had a fatal outcome. The data received during the reporting period is consistent with the characterization of this risk, and no further safety measures are deemed necessary.

16.3.1.5. Thrombocytopenia (Including Immune Thrombocytopenia)

Introduction

According to the cRMP (version 8.0, dated 06 February 2024) and EU RMP (version 7.1, dated 13 June 2023) ITP is an important identified risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

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

The case definition for this topic is described as follows: cases that were retrieved from the database were individually reviewed and cases meeting criteria for aggregate presentation were those that reported an EOI within the risk window of 42 days (or those where risk window was not reported), and an identifiable patient with evidence of thrombocytopenia. All cases were reviewed for evidence of thrombocytopenia per the interim Brighton Collaboration (BC) case definition version 10.16.3 for thrombocytopenia (Brighton Collaboration 2021a). It should be noted that there are no BC criteria for ITP. Cases were then further screened using a case definition modified from the American Society of Haematology (ASH) (Kelton 2018), and only cases meeting the definition for confirmed, likely, and suspected were included. It is acknowledged that the threshold appears very high for a case to be able to fulfil the definition of "confirmed" (see Table 64).

Table 64: Summary of ASH Case Definition for Immune Thrombocytopenia

	Platelet	Treatment	Antiplatelet Autoantibody Test	Causes of Thrombocytopenia (Clinical Manifestations)
Confirmed	A platelet count $<100x10^9$/L, with the exclusion of other causes of thrombocytopenia AND a low platelet count nadir ($<20x10^9$/L)	AND a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	AND a positive antiplatelet autoantibody test	(Exclusion of other causes of thrombocytopenia)

Table 64: Summary of ASH Case Definition for Immune Thrombocytopenia

	Platelet	Treatment	Antiplatelet Autoantibody Test	Causes of Thrombocytopenia (Clinical Manifestations)
Likely	A platelet count $<100x10^9/L$ OR a low platelet count nadir ($<20x10^9/L$)	OR a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	OR a positive antiplatelet autoantibody test	AND with the exclusion of other causes of thrombocytopenia
Suspect	-	-	-	Reported thrombocytopenia without a reported underlying or associated cause
Excluded	-	-	-	No thrombocytopenia secondary to other disease (e.g., tumour)

Key: ASH=American Society of Haematology; IVIG=Intravenous Immunoglobulin

Results/Discussion

Primary Dose

During this reporting interval, a total of 11 (9 medically confirmed and 2 medically unconfirmed) initial, primary dose cases reporting thrombocytopenia, including immune thrombocytyopenia were retrieved. These 11 serious cases reported a total of 11 serious EOIs. Out of these 11 cases, 2 cases were assessed as ITP cases per ASH case definition.

Cumulatively, 1,805 (1,572 medically confirmed and 233 medically unconfirmed), primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. There were 854 serious and 951 nonserious cases, which reported a total of 1972 EOI (930 serious, 1042 nonserious). Out of 1,805 cases, 550 cases were assessed as ITP cases per ASH case definition.

An overview of these cases is presented in Table 65.

Table 65: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Thrombocytopenia, Including Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=550
Sex	Male		308
	Female	2	237
	NR		5
Age (Years)[b]	18 to 35		78
Minimum: NR	36 to 50	1	169
Maximum:NR	51 to 64		145
Mean: NA	≥65		93
Median: NA	Adult		9
	NR	1	56

Table 65: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Thrombocytopenia, Including Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=550
Source	Spontaneous	2	427
	Clinical Trials		118
	Clinical Study (non-interventional, solicited)		4
	Clinical Study (non-interventional, unsolicited)		1
Country/Territory[c]	US	1	258
	Korea, Republic of		87
	Germany		45
	Spain	1	26
	South Africa		19
	France		17
	Brazil		12
	Italy		12
	Netherlands		12
	Colombia		9
	Philippines		8
	Austria		7
	Belgium		4
	Bulgaria		3
	Portugal		3
	Slovenia		3
Event Characteristics		**Number of Events=2**	**Number of Events=615**
Seriousness (Event Level)[d]	Serious	2	389
	Nonserious		226
Outcome (Event Level)[d]	Not resolved		176
	Resolved		159
	Resolving	1	57
	Fatal		18
	Resolved with sequelae		6
	NR	1	199

Key: EOI=Event of Interest; NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative data.

b: The median and mean age calculation could not be calculated for cases reported during current reporting interval as only 1 case reported age and the other case did not report any age, for calculation at least 2 entries are required.

c: Countries with frequency of ≥3 cumulatively have been presented.

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

Of the 2 cases received and included for review during the reporting interval, the countries/territories of origin were Spain and US (n=1 each). These cases concerned 2 females, one that was [redacted] years old and the other did not report age.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 66.

Table 66: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Assessed as Thrombocytopenia, including Immune ThrombocytopeniaWith the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia			159	93
Platelet count decreased			119	55
Thrombocytopenic purpura			11	78
Immune thrombocytopenia	2		88	
Thrombotic thrombocytopenic purpura			6	
Thrombosis with thrombocytopenia syndrome			5	
Platelet production decreased			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the interval data.
b: A single case may report more than 1 MedDRA PT of interest.

The EOIs reported during the reporting interval included immune thrombocytopenia (n=2). The TTO was not reported in these 2 cases. Of the 2 events, outcomes were reported as resolving (n=1), and unknown (n=1).

Booster Dose

During this reporting interval, 1 initial medically confirmed case reported as booster was identified. This case concerned multiple unidentifiable patients and provided limited information regarding the individual patient identifiers which precluded an adequate medical assessment. Hence, this case was not considered for further discussion.

Cumulatively, 287 (276 medically confirmed and 11 medically unconfirmed) cases reported as booster were identified. There were 29 serious and 258 nonserious cases, which reported a total of 289 EOIs (24serious and 265 nonserious). Out of 287 cases, 89 cases were assessed as ITP cases per the ASH case definition.

An overview of these cases is presented in Table 67

Table 67: Characteristics of Booster Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Thrombocytopenia, Including Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Reporting Interval=0	Number of Cases Received Cumulatively=89
Sex	Male		60
	Female		29
Age (Years)[a]	18 to 35		5
Minimum: NR	36 to 50		9
Maximum: NR	51 to 64		27
Mean: NA	≥65		18
Median: NA	Adult		4
	Elderly		1
	NR		25
Source	Spontaneous		14
	Clinical Study (non-interventional solicited)		3
	Clinical Study (interventional unsolicited)		72
Country/Territory	US		39
	South Africa		21
	Brazil		9
	Colombia		5
	Germany		4
	Belgium		2
	Philippines		2
	Chile		1
	France		1
	Greece		1
	Peru		1
	Portugal		1
	Spain		1
	United Kingdom		1
Classification	Homologous		79
	Heterologous		10
Event Characteristics		**Number of Events=0**	**Number of Events=90**
Seriousness (Event Level)[b]	Serious		10
	Nonserious		80
Outcome (Event Level)[b]	Resolved		50
	Not resolved		18
	Resolving		9
	Fatal		2
	NR		11

Key: EOI=Event of Interest; NR=Not Reported; US=United States

a: Since no cases were reported in the reporting interval, the median and mean age could not be calculated.

Table 67: Characteristics of Booster Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Thrombocytopenia, Including Immune Thrombocytopenia

Case Characteristics	Number of Cases Received During the Reporting Interval=0	Number of Cases Received Cumulatively=89

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

No cases assessed as ITP cases per the ASH case definition were received during the reporting interval.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 68.

Table 68: Frequency Distribution of MedDRA PTs of Interest in Booster Dose Cases Assessed as Thrombocytopenia, Including Immune ThrombocytopeniaWith the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia			3	62
Platelet count decreased			3	18
HELLP syndrome			1	
Immune thrombocytopenia			1	
Thrombosis with thrombocytopenia syndrome			1	
Thrombotic thrombocytopenic purpura			1	

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

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.10.1 and Appendix 6.10.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 639 case reports meeting the ASH definition of ITP have been received by the Company, of

which 15 had a fatal outcome. The data received during the reporting period is consistent with the characterization of this risk, and no further safety measures are deemed necessary.

16.3.2. New Information on Important Potential Risks

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

Introduction

According to the cRMP (version 8.0; dated 06 February 2024) and EU RMP (version 7.1, dated 13 June 2023), vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) is an important potential risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

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

Results/Discussion

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during this reporting interval.

Cumulatively, 1 medically confirmed, post-marketing, primary dose case reporting VAED, including VAERD was retrieved from the search. This case reported 1 serious EOI of antibody-dependent enhancement, and the outcome was not reported.

Booster Dose

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

Literature ICSR

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

Conclusion

Cumulatively (primary and booster) since launch till expiry of the last released doses, a single case of reported VAED including VAERD has been received by the Company. No cases were received during this reporting period. The data received during the reporting period is consistent with the characterization of this risk, and no further safety measures are deemed necessary. .

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

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

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

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

16.3.5. Update on Missing Information

In the FAR, for the Ad26.COV2.S PBRER dated 25 February 2022 to 24 August 2022, circulated on 14 April 2023 (PRAC AR 2023) (procedure number: EMEA/H/C/PSUSA/00010916/202208), the PRAC Rapporteur indicated that,

"The section 'Update on special patient populations', i.e. pregnancy/breastfeeding; Use in immunocompromised patients; Use in patients with autoimmune or inflammatory disorders; Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal".

These sections will not be included within this PBRER and future PBRERs unless the reporting pattern changes and/or there is a safety issue/signal. Separate subsections are found in the Appendices below for those markets requiring this information.

16.3.5.1. Use During Pregnancy

Information on this topic is found in Appendix 6.11.

16.3.5.2. Use in breastfeeding women

Information on use in breastfeeding women is found in Appendix 6.11.

16.3.5.3. Use in immunocompromised patients

Information on this topic is found in Appendix 6.12.

16.3.5.4. Use in patients with autoimmune or inflammatory disorders

Information on this topic is found in Appendix 6.13.

16.3.5.5. Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Information on this topic is found in Appendix 6.14.

16.3.5.6. Interaction With Other Vaccines

Information on interaction with other vaccines has been presented in Section 15.3, Use With Concomitant Vaccination.

16.3.5.7. Long-term safety

Information on this topic is found in Appendix 6.15.

16.3.6. Adverse Events of Special Interest

16.3.6.1. Cardiac Disorders

16.3.6.1.1. Cardiomyopathy

Introduction

Cardiomyopathy is listed as an AESI in the cRMP (version 8.0; dated 06 February 2024), EU RMP (version 7.1; dated 13 June 2023).

Methods

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

After the DLP of the last PBRER (24 February 2024), the Company has not been able to receive further exposure data from various countries/regions. Similarly, the Company cannot perform further RWE rapid cycle analysis following the withdrawal from the US prior to the reporting interval. Therefore, the Company cannot perform an Observed/Expected analysis.

Results/Discussion

Primary Dose

During this reporting interval, a total of 2 medically unconfirmed, initial primary dose cases reporting cardiomyopathy were retrieved. Both cases were serious and reported a total of 2 serious EOI.

Cumulatively, 87 (57 medically confirmed and 30 medically unconfirmed) primary dose cases reporting cardiomyopathy were retrieved. One case was excluded from further discussion since it involved multiple patients with no patient identifiers. Of the remaining 86 cases (57 medically confirmed and 29 medically unconfirmed), there were 85 serious and 1 nonserious case which reported a total of 95 EOI (91 serious; 4 nonserious). A single case may report more than 1 EOI.

An overview of these cases is presented in Table 69.

Table 69: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cardiomyopathy

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=86
Sex	Male	1	59
	Female	1	26
	NR		1
Age (Years)[b]	18 to 35	2	13
Minimum: 20	36 to 50		20
Maximum: 22	51 to 64		28
Mean: 21	≥65		23
Median: 21	Adult		1
	Elderly		1
Sources	Spontaneous	2	78
	Clinical Trial		8
Country/Territory	US		51
	Germany	1	18
	France		4
	Belgium		3
	Brazil		2
	Argentina		1
	Czech Republic		1
	Italy		1
	Latvia		1
	Netherlands		1
	Philippines		1
	Slovak Republic	1	1
	South Africa		1
Event Characteristics		**Number of Events=2**	**Number of Events=95**
Seriousness (Event Level)[c]	Serious	2	91
	Nonserious		4
Outcome (Event Level)[c]	Not resolved		34
	Resolved		18
	Fatal		12
	Resolving	1	9
	Resolved with sequelae		3
	NR	1	19

Key: EOI=Event of Interest; NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). Age group was presented for cases where age was not reported.

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

The 2 primary dose cases retrieved during the reporting interval were reported from Slovak Republic and Germany. These cases concerned 1 male and 1 female, aged [redacted] and [redacted] years, respectively.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 70.

Table 70: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Cardiomyopathy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Ejection fraction decreased	1		22	2
Cardiomyopathy			23	
Dilated cardiomyopathy			11	
Stress cardiomyopathy	1		8	
Ischaemic cardiomyopathy			7	
Cardiac hypertrophy			4	2
Hypertrophic cardiomyopathy			4	
Myocardial fibrosis			4	
Cardiomyopathy acute			2	
Cardiac amyloidosis			1	
Cardiac sarcoidosis			1	
Eosinophilic myocarditis			1	
Giant cell myocarditis			1	
Toxic cardiomyopathy			1	
Viral cardiomyopathy			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order based on the cumulative counts.
b: A single case may report more than 1 MedDRA PT of interest.

The EOI included ejection fraction decreased and stress cardiomyopathy (n=1 each). Where reported, the TTO was 426 days (n=1). The outcome of 1 EOI was resolving and the outcome of the other EOI was not reported.

Booster Dose

During this reporting interval, no initial case reported as booster was identified.

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

An overview of these cases is presented in Table 71.

Table 71: Characteristics of Booster Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cardiomyopathy

Case Characteristics		Number of Cases Received During the Reporting Interval=0	Number of Cases Received Cumulatively=5
Sex	Male		3
	Female		1
	NR		1
Age (Years)[a] **Minimum: NA** **Maximum: NA** **Mean: NA** **Median: NA**	18 to 35		
	36 to 50		2
	51 to 64		1
	≥65		1
	Adult		
	Elderly		
	NR		1
Sources	Spontaneous		5
Country/Territory	US		3
	Germany		1
	Spain		1
Classification	Heterologous		4
	Homologous		1
Event Characteristics		**Number of Events=0**	**Number of Events=5**
Seriousness (Event Level)[b]	Serious		5
Outcome (Event Level)[b]	Not resolved		1
	Resolving		1
	NR		3

Key: EOI=Event of Interest; NA=Not Applicable; NR=Not Reported; US=United States
a: Since no cases were reported during the current reporting interval(25 February 2024 to 30 September 2024), the mean and median age are not applicable.
b: Seriousness and outcome have been presented for the EOI.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 72.

Table 72: Frequency Distribution of MedDRA PTs of Interest in Booster Dose Cases Reporting Cardiomyopathy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cardiomyopathy			3	
Ejection fraction decreased			1	
Hypertrophic cardiomyopathy			1	

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

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.16.1 and Appendix 6.16.2, respectively.

Of the 2 primary dose cases received in this interval, the missing information on medical history/concurrent conditions, concomitant medications, clinical course, treatment, and outcome precluded meaningful causality assessment. Where reported, the TTO was 426 days. No literature articles were identified during the interval. Overall, no specific patterns among cases reporting cardiomyopathy were identified.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 91 case reports of Cardiomyopathy have been received by the Company, of which 12 had a fatal outcome. However, based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Cardiomyopathy.

16.3.6.2. Nervous System Disorders

16.3.6.2.1. Encephalitis, Including Acute Disseminated Encephalomyelitis (ADEM) and Meningoencephalitis

Introduction

Encephalitis, including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis is listed as an AESI in the cRMP (version 8.0; dated 06 February 2024), EU RMP (version 7.1; dated 13 June 2023).

Methods

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

After the DLP of the last PBRER (24 February 2024), the Company has not been able to receive further exposure data from various countries/regions. Similarly, the Company cannot perform further RWE rapid cycle analysis following the withdrawal from the US prior to the reporting interval. Therefore, the Company cannot perform an Observed/Expected analysis.

Results/Discussion

Primary Dose

During this reporting interval, a total of 3 (1 medically confirmed and 2 medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All cases were assessed as serious which reported a total of 3 serious EOI.

Cumulatively, 108 (75 medically confirmed and 33 medically unconfirmed) primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. Six cases were excluded from further discussion since these involved multiple patients with no patient identifiers. Of the remaining 102 cases (69 medically confirmed and 33 medically unconfirmed), all cases were assessed as serious which reported a total of 108 serious EOI. A single case may report more than 1 EOI.

An overview of these cases is presented in Table 73.

Table 73: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=102
Sex	Male	2	52
	Female		47
	NR	1	3
Age (Years)[b]	<18		2
Minimum: 25	18 to 35	2	28
Maximum: 37	36 to 50	1	49
Mean: 32.3	51 to 64		9
Median: 35	≥65		10
	Adult		1
	NR		3
Sources	Spontaneous	3	97
	Clinical Trial		5
Country/Territory	US		27
	Korea, Republic of		23
	Germany	1	22
	South Africa		6
	France		4
	Romania		3
	Colombia		2
	Denmark		2
	Poland	1	2
	Spain		2
	Argentina		1
	Belgium		1
	Brazil		1
	Croatia		1
	Greece		1
	Italy		1
	Latvia	1	1
	Mexico		1
	Philippines		1
Event Characteristics		**Number of Events of Interest=3**	**Number of Events of Interest=108**
Seriousness (Event Level)[c]	Serious	3	108

Table 73: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=102
Outcome (Event Level)[c]	Not resolved	1	34
	Resolved		13
	Resolving	1	11
	Resolved with sequelae	1	8
	Fatal		3
	NR		39

Key: ADEM=Acute Disseminated Encephalomyelitis; EOI=Event of Interest; NR=Not Reported; US=United States

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). Age group was presented for cases where age was not reported.

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

The 3 primary dose cases retrieved during the reporting interval were reported from Poland, Latvia, and Germany. These cases concerned 2 males, and 1 case did not report sex. The age range was from 25 to 37 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 74.

Table 74: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Encephalitis, Including ADEM and Meningoencephalitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Encephalitis			48	
Acute disseminated encephalomyelitis	1		23	
Noninfective encephalitis			13	
Encephalomyelitis	1		10	
Encephalitis autoimmune			9	
Acute haemorrhagic leukoencephalitis			1	
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids			1	
Encephalitis haemorrhagic			1	
Encephalitis post immunisation			1	
Myelin oligodendrocyte glycoprotein antibody-associated disease	1		1	

Table 74: Frequency Distribution of MedDRA PTs of Interest in Primary Dose Cases Reporting Encephalitis, Including ADEM and Meningoencephalitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: ADEM=Acute Disseminated Encephalomyelitis; EOI=Event of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: For the interval (25 February 2024 to 30 September 2024) column, the EOI were presented in decreasing order based on the cumulative MedDRA PTs of interest. A single case may report more than 1 MedDRA PT of interest.

The EOI during the reporting interval, included acute disseminated encephalomyelitis, myelin oligodendrocyte glycoprotein antibody-associated disease, and encephalomyelitis (n=1 each). Where reported (n=1), the TTO was 689 days. The outcomes of the EOI were reported as follows: resolved with sequelae, resolving, and not resolved (n=1 each).

Booster Dose

During this reporting interval, no initial case reported as booster was identified.

Cumulatively, 3 (2 medically confirmed and 1 medically unconfirmed) cases reported as booster were retrieved. All cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were homologous and 1 was heterologous.

An overview of these cases is presented in Table 75.

Table 75: Characteristics of Booster Dose Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Reporting Interval=0	Number of Cases Received Cumulatively=3
Sex	Male		2
	Female		1
Age (Years)[a]	<18		
Minimum: NA	18 to 35		
Maximum: NA	36 to 50		1
Mean: NA	51 to 64		1
Median: NA	≥65		1
	Adult		
	NR		
Sources	Spontaneous		3
Country/Territory	Brazil		1
	Germany		1
	US		1
Classification	Homologous		2
	Heterologous		1

Table 75: Characteristics of Booster Dose Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Reporting Interval=0	Number of Cases Received Cumulatively=3
Event Characteristics		**Number of Events of Interest=0**	**Number of Events of Interest=3**
Seriousness (Event Level)	Serious		3
Outcome (Event Level)	Resolving		1
	NR		2

Key: ADEM=Acute Disseminated Encephalomyelitis; NA=Not Applicable; NR=Not Reported; US=United States

a: Since no cases were reported during the current reporting interval (25 February 2024 to 30 September 2024), the mean and median age are not applicable.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 76.

Table 76: Frequency Distribution of MedDRA PTs of Interest in Booster Dose Cases Reporting Encephalitis, Including ADEM and Meningoencephalitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval		Number of Events Reported Cumulatively	
	Serious	**Nonserious**	**Serious**	**Nonserious**
Acute disseminated encephalomyelitis			1	
Encephalitis			1	
Encephalitis autoimmune			1	

Key: ADEM=Acute Disseminated Encephalomyelitis; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.17.1 and Appendix 6.17.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 105 case reports of encephalitis, including ADEM and meningoencephalitis have been received by the Company, of which 07 had a fatal outcome. Based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is

insufficient evidence to establish a causal association between Ad26.COV2.S and Encephalitis, including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis.

16.3.6.2.2. Multiple Sclerosis (Including Optic Neuritis)

Introduction

Multiple sclerosis, including optic neuritis, is listed as an AESI in the cRMP (version 8.0, dated 06 February 2024).

Methods

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

After the DLP of last PBRER (24 February 2024), the Company has not been able to receive further exposure data from various countries/ regions. Similarly, the Company cannot perform any further RWE rapid cycle analysis following the withdrawal from the US prior to the reporting interval. Therefore, the Company cannot perform an Observed/Expected analysis.

Results/Discussion

Primary Dose

During this reporting interval, 1 medically confirmed, initial primary dose case reporting multiple sclerosis, including optic neuritis, was retrieved. This serious case was reported for a [redacted]-year-old female from Poland and reported a serious EOI of multiple sclerosis relapse. The TTO was reported as 0 day (same day). The outcome was not reported.

Cumulatively, 88 (46 medically confirmed and 42 medically unconfirmed), primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 88 cases were serious and reported a total of 92 serious EOI. A single case may report more than 1 EOI.

An overview of the interval and cumulative cases is presented in Table 77.

Table 77: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During Interval=1	Number of Cases Received Cumulatively=88
Sex	Female	1	46
	Male		35
	NR		7
Age (Years)[a]	18 to 35		22
Minimum: NA	36 to 50		37
Maximum: NA	51 to 64	1	15
Mean: NA	≥65		4
Median: NA	Adult		1
	NR		9

Table 77: Characteristics of Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During Interval=1	Number of Cases Received Cumulatively=88
Sources	Spontaneous	1	79
	Clinical Trial		5
	Clinical Study (solicited, non-interventional)		4
Country/Territory	US		44
	Germany		11
	Poland	1	5
	Czech Republic		4
	Greece		4
	Brazil		3
	Belgium		2
	France		2
	Italy		2
	Austria		1
	Hungary		1
	Ireland		1
	Mexico		1
	Netherlands		1
	Philippines		1
	Portugal		1
	Slovak Republic		1
	South Africa		1
	Spain		1
	Zambia		1
Event Characteristics		**Number of Event=1**	**Number of Events=92**
Seriousness (Event Level)[b]	Serious	1	92
Outcome (Event Level)[b]	Not resolved		51
	Resolved		9
	Resolved with sequelae		5
	Resolving		8
	NR	1	19

Key: EOI=Event(s) of Interest; NA=Not Applicable; NR=Not Reported; US=United States

a: The median and mean age calculation could not be calculated for cases reported during current reporting interval as only 1 case reported age and for calculation at least 2 entries are required.

b: 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 is presented in Table 78.

Table 78: Frequency Distribution of MedDRA PTs of Interest in Primary dose Cases Reporting Multiple Sclerosis, Including Optic Neuritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Event Reported During Interval	Number of Events Reported Cumulatively
Multiple sclerosis	1	42
Optic neuritis		33
Multiple sclerosis relapse		14
Primary progressive multiple sclerosis		1
Relapsing multiple sclerosis		1
Tumefactive multiple sclerosis		1
Grand Total		**92**

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

Booster Dose

During this reporting interval, no cases reported as booster were identified.

Cumulatively, 10 (4 medically confirmed and 6 medically unconfirmed) cases reported as booster were identified. All 10 cases were serious and reported a total of 12 serious EOI. Of these cases, 7 were heterologous and 3 were homologous. A single case may report more than 1 EOI.

An overview of the cumulative cases is presented in Table 79.

Table 79: Characteristics of Booster Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During Interval=0	Number of Cases Received Cumulatively=10
Sex	Male		7
	Female		3
Age (Years)[a]	18 to 35		5
Minimum: NA	36 to 50		2
Maximum:NA	51 to 64		1
Mean: NA	≥65		1
Median: NA	NR		1
Sources	Spontaneous		10
Country/Territory	Germany		5
	US		2
	Greece		1
	Italy		1
	Spain		1
Classification	Homologous		3
	Heterologous		7
Event Characteristics		**Number of Events=0**	**Number of Events=12**
Seriousness (Event Level)[b]	Serious		12
Outcome (Event Level)[b]	Not resolved		8
	Resolved with sequelae		2
	Resolving		1
	NR		1

Table 79: Characteristics of Booster Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics	Number of Cases Received During Interval=0	Number of Cases Received Cumulatively=10

Key: EOI=Event(s) of Interest; NA=Not Applicable; NR=Not Reported; US=United States
a: Since no cases were reported during the current reporting interval(25 February 2024 to 30 September 2024), the mean and median age are not applicable.
b: 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 is presented in Table 80.

Table 80: Frequency Distribution of MedDRA PTs of Interest in Booster dose Cumulative Cases Reporting Multiple Sclerosis, Including Optic Neuritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During Interval	Number of Events Reported Cumulatively=12
Optic neuritis		6
Multiple sclerosis		4
Leukoencephalopathy		1
Relapsing-remitting multiple sclerosis		1
Grand Total		**12**

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

Literature ICSR

During this reporting interval, no ICSR literature cases were received.

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.18.1 and Appendix 6.18.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 98 case reports of Multiple sclerosis, including optic neuritis have been received by the Company, of which 02 had a fatal outcome. Based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Multiple sclerosis, including optic neuritis..

16.3.6.2.3. Narcolepsy

Introduction

Narcolepsy is listed as an AESI in the cRMP (version 8.0, dated 06 February 2024).

In the second updated PRAC Rapporteur AR (PRAC AR 2023; procedure number EMEA/H/C/PSUSA/00010916/202208) for the Ad26.COV2.S PBRER dated 25 February 2022 to

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

Methods

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

After the DLP of last PBRER (24 February 2024), the Company has not been able to receive further exposure data from various countries/ regions. Similarly, the Company cannot perform any further RWE rapid cycle analysis following the withdrawal from the US prior to the reporting interval. Therefore, the Company cannot perform an Observed/Expected analysis.

Results/Discussion

Primary Dose

During this reporting interval, a total of 2 medically unconfirmed, initial primary dose cases reporting narcolepsy were retrieved. These 2 nonserious cases reported 2 nonserious EOI.

Cumulatively, 614 (85 medically confirmed and 529 medically unconfirmed) primary dose cases reporting narcolepsy were retrieved. There were 205 serious and 409 nonserious cases which reported a total of 624 EOI (102 serious, 522 nonserious). A single case may report more than 1 EOI.

An overview of these cases is presented in Table 81.

Table 81: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=614
Sex	Female	1	309
	Male	1	256
	NR		49
Age (Years)[b]	18 to 35		134
Minimum: 50	36 to 50	1	154
Maximum:55	51 to 64	1	159
Mean: 52.5	Adult		8
Median: 52.5	NR		89
Sources	Spontaneous	2	581
	Clinical study (non-interventional, solicited		32
	Clinical study (non-interventional, unsolicited		1

Table 81: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting Interval=2[a]	Number of Cases Received Cumulatively=614
Country/Territory[c]	US		305
	Germany	1	157
	Belgium		19
	Poland		18
	Netherlands		17
	Austria		12
	Spain		11
	France		9
	Ireland		9
	Switzerland		8
	Brazil		7
	Latvia		7
	Portugal		5
Event Characteristics		**Number of Events=2**	**Number of Events=624**
Seriousness (Event Level)[d]	Nonserious	2	522
	Serious		102
Outcome (Event Level)[d]	Not resolved	1	225
	Resolved		125
	Resolving		70
	Resolved with sequelae		14
	Fatal		1
	NR	1	189

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). Age group was presented for cases where age was not reported.

c: The countries/territories with frequency ≥5 were presented in decreasing order based on the cumulative column.

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

Of the 2 primary dose cases received during the reporting interval, the reported countries/territories of origin were Estonia and Germany (n=1 each). These cases concerned 1 female and 1 male. The age range was from 50 to 55 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 82.

Table 82: Frequency Distribution of MedDRA PTs of Interest in Primary dose Cases Reporting Narcolepsy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval [a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder		2	77	302
Hypersomnia			20	220
Narcolepsy			4	
Sudden onset of sleep			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The events were presented in decreasing order based on the cumulative column.

The EOI included sleep disorder (n=2). One case reported Time to Onset (TTO) of 31 days while TTO was not reported in other. Of the 2 EOI, outcome was reported for 1 as not resolved.

Booster Dose

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

Cumulatively, 56 (7 medically confirmed and 49 medically unconfirmed) cases reported as booster were retrieved. There were 21 serious and 35 nonserious cases which reported a total of 56 EOI (8 serious; 48 nonserious). Of these cases, 36 were heterologous and 20 were homologous.

An overview of these cases is presented in Table 83.

Table 83: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=56
Sex	Female		31
	Male	2	20
	NR	1	5
Age (Years)[b]	18 to 35		11
Minimum: NA	36 to 50		18
Maximum: NA	51 to 64	1	16
Mean: NA	≥65		5
Median: NA	NR	2	6
Sources	Spontaneous	3	44
	Clinical study (non-interventional, solicited)		12
Country/Territory	Germany	3	27
	US		15
	Brazil		5
	Canada		3
	Austria		2

Table 83: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=56
	Belgium		1
	Estonia		1
	Hungary		1
	Italy		1
Classification	Heterologous	3	36
	Homologus		20
Event Characteristics		**Number of Events=3**	**Number of Events=56**
Seriousness (Event Level)[c]	Nonserious	2	48
	Serious	1	8
Outcome (Event Level)[c]	Not resolved	2	19
	Resolved		9
	Resolving		8
	Resolved with sequelae		4
	NR	1	16

Key: NA=Not Applicable; NR=Not Reported; US=United States
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: The median and mean age calculations were based on the current reporting interval (25 February 2024 to 30 September 2024) and were not applicable since at least 2 data values are required for calculation and only 1 case reported age.
c: Seriousness and outcome have been presented based on the events of interest reported cumulatively. A single case may report more than 1 event of interest.

All the 3 cases reported during the reporting interval as booster were reported from Germany (n=3). These cases concerned 2 males while gender was not reported for 1 case. The age was reported in 1 case (59 years) and not reported in the remaining 2 cases.

The frequency distribution of the MedDRA PTs of interest reported in cases reported as booster is presented in Table 84.

Table 84: Frequency Distribution of MedDRA PTs of Interest in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Narcolepsy

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	1	2	6	35
Hypersomnia			1	13
Narcolepsy			1	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The events were presented in decreasing order based on the cumulative column.
b: A single case may report more than 1 MedDRA PT.

The EOI reported during the reporting interval included sleep disorder (n=3). The mean and

median TTO were not applicable as only 1 case reported latency (0 days). Of the 3 EOI, the outcomes were reported for 2 as not resolved (n=2).

Literature ICSR

During this reporting interval, no ICSR literature cases were received.

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.19.1 and Appendix 6.19.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 670 case reports of Narcolepsy have been received by the Company, of which 04 had a fatal outcome. However, based on the totality of the safety data available to the Company at the time of the vaccine's marketing 134uthorization withdrawal, there is insufficient evidence to establish a causal association between Ad26.COV2.S and Narcolepsy.

16.3.6.3. Vascular Disorders

16.3.6.3.1. Cerebrovascular Events

Introduction

Cerebrovascular events are listed as an AESI in the cRMP (version 8.0, 06 February 2024), EU RMP(version 7.1, dated 13 June 2023). The Company opened a signal on haemorrhagic cerebrovascular events- based on disproportionate reporting in WHO's VigiBase, however this signal was closed in the previous PBRER with the reporting interval of 25 February 2023 to 24 February 2024.

Methods

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

After the DLP of last PBRER (24 February 2024), the Company has not been able to receive further exposure data from various countries/ regions. Similarly, the Company cannot perform any further RWE rapid cycle analysis following the withdrawal from the US prior to the reporting interval. Therefore, the Company cannot perform an Observed/Expected analysis.

Results/Discussion

Primary Dose

During this reporting interval, a total of 15 (6 medically confirmed and 9 medically unconfirmed) initial, primary-dose cases reporting cerebrovascular events were retrieved. All of these 15 cases were serious and reported a total of 19 EOI (18 serious, 1 nonserious).

Cumulatively, 1,923 (1,205 medically confirmed and 718 medically unconfirmed) primary-dose cases reporting cerebrovascular events were retrieved. There were 1,909 serious and 14 nonserious cases which reported a total of 2,456 EOI (2,438 serious; 18 nonserious). A single case may report more than 1 EOI.

An overview of these cases is presented in Table 85.

Table 85: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=15[a]	Number of Cases Received Cumulatively=1,923
Sex	Female	7	975
	Male	6	871
	NR	2	77
Age (Years)[b]	0 to 17		3
Minimum: 18	18 to 35	2	201
Maximum:78	36 to 50	4	414
Mean: 46.1	51 to 64	1	593
Median: 47	≥65	2	529
	Neonate		2
	Adult		5
	Elderly	1	5
	NR	5	171
Sources	Spontaneous	12	1,661
	Clinical Trial	1	235
	Clinical Study (non-interventional, solicited)	2[c]	26
	Clinical Study (non-interventional, unsolicited)		1
Country/Territory[d]	US	8	1,233
	Germany	2	176
	South Africa		69
	Philippines		67
	France		47
	Italy		46
	Netherlands		45
	Brazil		33
	Poland	1	24
	Spain		24
	Belgium		20
	Austria	1	12
	Greece		12
	Colombia		11
	Argentina		10
	Portugal		9
	Czech Republic		7
	Romania		7

Table 85: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=15[a]	Number of Cases Received Cumulatively=1,923
	Slovenia		7
	Estonia		6
	Latvia		6
	Ireland		5
	Peru		5
	United Kingdom	1	5
Event Characteristics		**Number of Events=19**	**Number of Events=2,456**
Seriousness (Event Level)[c]	Serious	18	2,438
	Nonserious	1	18
Outcome (Event Level)[c]	Not resolved	2	748
	Resolved	6	646
	Resolving		219
	Fatal		201
	Resolved with sequelae		78
	NR	11	564

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

A: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculation were based on the current reporting interval (25 February 2024 to 30 September 2024). For cases where age was not reported, age group has been presented.

c: Counts include 1 from literature source.

d: The countries/territories with frequency ≥5 were presented in decreasing order based on the cumulative column.

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

Of these 15 primary-dose cases received during the reporting interval, the most frequently reported country/territory of origin was the US (n=8). These cases concerned 7 females, 6 males, and 2 cases that did not report sex. The age range was from 18 to 78 years.

The frequency distribution of the MedDRA PTs of interest reported is presented Table 86.

Table 86: Frequency Distribution of MedDRA PTs of Interest in Primary-dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Cerebrovascular accident	9		615	2
Intracranial aneurysm	1		295	
Transient ischaemic attack	1		156	6
Hemiparesis	1		159	
Ischaemic stroke			149	1
Cerebral venous sinus	1		128	

Table 86: Frequency Distribution of MedDRA PTs of Interest in Primary-dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
thrombosis				
Cerebral infarction	1		114	
Cerebral haemorrhage	2		106	
Hemiplegia			74	
Cerebral thrombosis			68	
Haemorrhagic stroke			38	
Cerebral venous thrombosis			34	
Subarachnoid haemorrhage	1		30	
Transverse sinus thrombosis			26	
Cerebral artery occlusion			20	
Carotid artery thrombosis			19	
Cerebral ischaemia			18	1
Subdural haematoma			18	
Superior sagittal sinus thrombosis			17	1
Cerebrovascular disorder		1	14	3
Haemorrhage intracranial			17	
Hemiparaesthesia			16	
Embolic stroke			15	
Carotid artery stenosis			14	
Lacunar infarction			14	
Carotid artery occlusion			12	
Cerebral small vessel ischaemic disease			12	
Ischaemic cerebral infarction			11	1
Cerebellar infarction			11	
Cerebral artery thrombosis	1		11	
Hemihypoaesthesia			11	
Thalamic infarction			10	

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.
b: Frequency of MedDRA PTs of interest were with frequency ≥10 have been presented for cumulative data. A single case may report more than 1 MedDRA PT.

The EOI reported during the reporting interval at a frequency >2 included cerebrovascular accident (n=9). The mean and median TTO were 121.6 and 110 days, respectively, and the range was from 3 to 537 days. Of the 19 EOI, outcomes were reported for 8 as follows: resolved (n=6), and not resolved (n=2).

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

During this reporting interval, no fatal (primary dose and booster) case was reported in patients ≤40 years of age. A total of 5 non-fatal (4 primary dose and 1 case reported as booster) cases were

reported in patients ≤40 years of age. Information for these cases which occurred in patients ≤40 years of age is included in Appendix 6.20.

Of the 5 non-fatal cases, the EOI was outside the 28-day risk window in 2 cases (all primary dose). The remaining 3 cases (2 primary dose cases and 1 booster dose case) lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. Case information for the 5 non-fatal cases that occurred in patients ≤40 years of age are included in Appendix 6.20.

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting interval did not identify evidence suggestive of cerebrovascular events being causally associated with Ad26.COV2.S.

Booster Dose

During this reporting interval, a total of 3 (1 medically confirmed and 2 medically unconfirmed) cases reported as booster were identified. All of these 3 cases were serious and reported a total of 3 events (all serious). Of these cases, 2 were heterologous and 1 was homologous.

Cumulatively, 84 (44 medically confirmed and 40 medically unconfirmed) cases reported as booster were retrieved. There were 82 serious and 2 nonserious cases which reported a total of 111 EOI (108 serious; 3 nonserious). Of these cases, 28 were heterologous and 56 were homologous. A single case may report more than 1 EOI.

An overview of these cases is presented in Table 87.

Table 87: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=84
Sex	Male	2	47
	Female		31
	NR	1	6
Age (Years)[b]	18 to 35	1	8
Minimum: 34	36 to 50	1	17
Maximum:47	51 to 64		29
Mean: 40.5	≥65		16
Median: 40.5	Adult		1
	NR	1	13
Sources	Spontaneous	3[c]	77
	Clinical Study (non-interventional,solicited)		3
	Clinical Study		2

Table 87: Characteristics of Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=3[a]	Number of Cases Received Cumulatively=84
	(non-interventional,nonsolicited)		
	Clinical Trial		2
Country/Territory	US	2	47
	Germany	1	15
	Brazil		7
	South Africa		4
	Greece		2
	Philippines		2
	Colombia		1
	Ireland		1
	Netherlands		1
	Slovenia		1
	Spain		1
	Switzerland		1
	United Kingdom		1
Classification	Heterologous	2	28
	Homologous	1	56
Event Characteristics		**Number of Events=3**	**Number of Events=111**
Seriousness (Event Level)[d]	Serious	3	108
	Nonserious		3
Outcome (Event Level)[d]	Resolved		16
	Not resolved	2	21
	Fatal		16
	Resolving		9
	Resolved with sequelae		4
	NR	1	45

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

a: For the interval (25 February 2024 to 30 September 2024) column, the counts were presented in decreasing order based on the cumulative counts.

b: The median and mean age calculations were based on the current reporting interval (25 February 2024 to 30 September 2024). Age group was presented for cases where age was not reported.

c: Cases included 1 from literature source.

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

Among these 3 cases reported as booster during the reporting interval, the reported country/territory of origin was the US (n=2), followed by Germany (n=1). These cases concerned 2 males, and 1 case that did not report sex. The age range was from 34 to 47 years.

The frequency distribution of the MedDRA PTs of interest reported in cases reported as booster is presented in Table 88.

Table 88: Frequency Distribution of MedDRA PTs of Interest in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Cerebrovascular accident	1		39	
Transient ischaemic attack			9	
Ischaemic stroke			7	
Cerebral infarction			6	1
Hemiparesis			6	
Cerebral thrombosis			5	
Cerebral venous sinus thrombosis	1		5	
Cerebral haemorrhage			3	
Embolic stroke	1		3	
Subarachnoid haemorrhage			3	
Cerebrovascular disorder				2
Haemorrhagic stroke			2	
Hemiplegia			2	
Lacunar stroke			2	

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The events were presented in decreasing order based on the cumulative column.
b: Frequency of MedDRA PTs of interest were with frequency ≥2 have been presented for cumulative data. A single case may report more than 1 EOI.

The EOI reported during the reporting interval were Cerebral venous sinus thrombosis, Cerebrovascular accident, Embolic stroke (n=1 each). The TTO was reported in one case as 3 days and rest of two cases TTO was not reported. Of the 3 EOI, the outcomes were reported for 2 as not resolved.

Literature ICSR

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

Line Listings

Primary and Booster: The interval CIOMS II LL of cases reported as primary and booster is presented in Appendix 6.20.1. and Appendix 6.20.2, respectively.

Conclusion

Cumulatively (primary and booster) since launch till the expiry of the last released doses, a total of 2,007 case reports of Cerebrovascular events have been received by the Company, of which 220 had a fatal outcome. Cerebrovascular events may occur very rarely as a complication of TTS, VTE or ITP following vaccination. However, based on the totality of the safety data available to the Company at the time of the vaccine's marketing authorisation withdrawal, there is insufficient

evidence to establish a causal association between Ad26.COV2.S and spontaneous Cerebrovascular events (ischemic or hemorrhagic). .

16.3.6.4. Death

As per PRAC confirmation received in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (25 August 2021 to 24 February 2022) (EMEA/H/C/PSUSA/00010916/202202) dated 29 September 2022: A separate death subsection with interval and cumulative death cases is no longer required to be presented in the report body of this PBRER or in future PBRERs. However, a separate subsection is found in Appendix 6.21 for those regions requiring this information.

16.4. Characterisation of Risks

The overall current safety profile of the Ad26.COV2.S vaccine was established based on the cumulative spontaneous reports from the Company global safety database on an approximate exposure of 53,288,029 (CDC [2022], ECDC [2022], KDCA [2022]), and available clinical trial data. 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 current cRMP (version 8.0; dated 06 February 2024) was used as a reference for this section.

Important risks identified during clinical studies or post-marketing experience of Ad26.COV2.S include:

Thrombosis With Thrombocytopenia Syndrome

Potential Mechanisms:

The exact mechanism of TTS following vaccination with Ad26.COV2.S is unknown. Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of vaccine-induced TTS, including vaccine-mediated induction of platelet-activating antibodies directed against the cationic platelet chemokine PF4 (CXCL4), subsequently referred to as anti-PF4 antibodies (Greinacher 2021).

The Company assessed a possible interaction between PF4 and Ad26.COV2.S and does not have conclusive evidence for binding of Ad26.COV2.S to PF4 in vitro. Several research teams in the TTS field are pursuing to investigate the potential binding of different adenovirus vectors or other components in the formulation of the COVID-19 vaccines to PF4. The Company will continue to follow the research developments regarding the potential binding to PF4 and support those activities wherever possible.

Besides the adenovirus vector, a potential role of the S protein as well as of a predisposition of the patient should be considered. The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis

(Robles 2022; Lei 2021; Perico 2022; Zhang 2020; Grobbelaar 2021; Zheng 2021; Lee 2023), and is hypothesised to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

With the remaining ongoing additional pharmacovigilance activities, the Company aims to further understand what the potential causes of TTS might be and to gain insights into possible anti-PF4 antibody induction in the context of post-vaccination TTS.

Evidence Source(s) and Strength of Evidence:

Thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S and is an adverse drug reaction described in the CCDS.

Characterisation of the Risk:

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcomes have been reported. These cases occurred within the first 3 weeks following vaccination, and mostly in individuals <60 years of age.

In the cRMP (version 8.0, 06 February 2024), for purposes of TTS risk characterisation and presentation of cases, 3 case definitions are used: the interim BC case definition (Brighton Collaboration 2021), the CDC working case definition for a Tier 1 or Tier 2 case (Shimabukuro 2021), and the PRAC case definition, which is based on the one proposed by the UK's National Institute for Health and Care Excellence (NICE) (NICE 2022).

An update on the number of cases of TTS from clinical trial and post-marketing experience is provided in Section 16.3.1.1, Thrombosis with Thrombocytopenia Syndrome of this PBRER.

Risk Factors and Risk Groups:

Although no clear risk factors have been identified, the cases of thrombosis in combination with thrombocytopenia reported in the post-marketing setting more commonly occurred in women aged <50 years.

Preventability:

Thrombosis with thrombocytopenia syndrome requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (eg, haematologists, specialists in coagulation) to diagnose and treat this condition (CCDS Section Warnings and Precautions).

The CCDS (Section Contraindications) states that Ad26.COV2.S is contraindicated in individuals with a history of confirmed TTS following vaccination with any COVID-19 vaccine. The CCDS

(Section Warnings and Precautions) makes reference to this contraindication and states that individuals who have experienced heparin-induced thrombocytopenia should only receive Ad26.COV2.S if the potential benefits outweigh the potential risks. Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain or swelling, or progressive abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with Ad26.COV2.S should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

Impact on the Risk-Benefit Balance of the Product:

Thrombosis in combination with thrombocytopenia after vaccination with Ad26.COV2.S is a very rare event which is potentially life-threatening, especially if improperly managed. Adequate risk minimisation that raises public awareness and supports education of healthcare professionals may lead to earlier diagnosis and appropriate treatment, which may improve the prognosis of TTS. Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

The occurrence of TTS is very rare following vaccination with Ad26.COV2.S. Therefore, the impact on public health is expected to be low.

Guillain-Barré Syndrome

Potential Mechanisms:

The mechanism of Ad26.COV2.S-related GBS has not been established. However, as with other vaccines, immune activation is believed to play a role in the development of the disease (Sejvar 2011).

Evidence Source(s) and Strength of Evidence:

Guillain-Barré syndrome has been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials, and in the post-marketing setting (Hanson 2022; Miriam 2022). Similar AEs have also been described following administration of other COVID-19 vaccines. Despite no clear biological mechanism being identified, the Company considers the increase in observed versus expected ratios since authorisation to be sufficient evidence for a plausible association between Ad26.COV2.S and GBS.

Guillain-Barré Syndrome is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of GBS from clinical trial and post-marketing experience is provided in Section 16.3.1.2, Guillain-Barré Syndrome of this PBRER.

Risk Factors and Risk Groups:

There are no known risk factors for the development of GBS following Ad26.COV2.S vaccination. Based mainly on data from North America and Europe, it has been shown in literature that the GBS incidence increased by 20% for every 10-year increase in age; GBS is usually more frequent in males, with the highest incidence between 50 to 70 years of age (Van Doorn 2020).

Preventability:

The CCDS (Section Warnings and Precautions) states that healthcare professionals should be alert to GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes.

Impact on the Risk-Benefit Balance of the Product:

Although GBS is a serious event that has been reported following vaccination with Ad26.COV2.S, it has been reported at a very low incidence and adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Therefore, the impact on the risk-benefit balance for the vaccine is considered to be low.

Public Health Impact:

Guillain-Barré Syndrome associated with vaccines typically occurs at a low incidence, resulting in a low public health impact. Although the potential clinical consequences of GBS are serious, this is a risk known to healthcare professionals, with negligible public health impact.

Venous Thromboembolism

Potential Mechanisms:

A potential mechanism for the occurrence of VTE includes a hypercoagulable state due to an increased pro-inflammatory response to vaccination. Activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles can trigger the coagulation system through the induction of tissue factor (Branchford 2018). An underlying mechanism for VTE without thrombocytopenia has not been confirmed. Natural infection with SARS-CoV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and VTE or arterial thrombosis (Ribes 2020).

The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Grobbelaar 2021; Lei 2021; Perico 2022; Robles 2022; Zhang 2020; Zheng 2021), and is hypothesised to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

Recent mechanistic studies (non-clinical studies, and studies using clinical trial samples) conducted by the Company to study the pathogenesis of (vaccine-induced) TTS with potential relevance to VTE, did not elucidate a clear mechanism of action (MOA) for VTE following Ad26.COV2.S administration. However, in the context of the Company's mechanistic work on TTS, the hypothesis was tested if TTS and other thrombotic events could have a common mechanism with TTS being the most severe manifestation. Obtained data suggest that a common mechanism is unlikely.

Evidence Source(s) and Strength of Evidence:

Venous thromboembolism has been observed rarely following vaccination with Ad26.COV2.S in clinical trials and in the post-marketing setting. While a higher proportion of cases of VTE was observed within the Ad26.COV2.S group versus the Placebo group in Trial COV3001, there was no increase in VTE events among individuals who received Ad26.COV2.S in Trial COV3009.

Venous thromboembolism is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of VTE from clinical trial and post-marketing experience is provided in Section 16.3.1.3, Venous Thromboembolism of this PBRER.

Risk Factors and Risk Groups:

In Trials COV3001 and COV3009, underlying risk factors have been identified in subjects with VTE such as COVID-19, male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, active malignancy, trauma, previous venous thrombosis, hypertension, and COPD.

Preventability:

The CCDS (Section Warning and Precautions) provides guidance to healthcare professionals to be alert to the signs and symptoms of thromboembolism.

Impact on the Risk-Benefit Balance of the Product:

Venous thromboembolism is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. Adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of VTE events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

Myocarditis and Pericarditis

Potential Mechanisms:

Infectious diseases account for the majority of cases of myocarditis or pericarditis in previously healthy patients, mainly due to either a direct viral infection or post-viral immune-mediated reaction and myocardial inflammation (Friedrich 2009) and is more frequent in young males. Also viral infection with SARS-CoV-2 can result in acute myocarditis, yet COVID-19 vaccination (including mRNA vaccines and Ad26.COV2.S) was associated with decreased risk of myocarditis, myocardial infarction, and ischaemic stroke after COVID-19 (Jiang 2023; Kim 2024; Patone 2022).

The MOA for vaccine-induced myopericarditis remains to be elucidated. Given the increased incidence among males, differences in hormone signaling might be involved in the pathophysiology (Heymans 2022). It has been proposed that vaccines triggering an intense immune response could be associated with a higher risk of myocarditis (Karlstad 2022). Also, a possible association of circulating S protein with the occurrence of myocarditis has been described (Yonker 2023). Molecular mimicry between the S protein of SARS-CoV-2 and cardiac self-antigens is another possible mechanism. However, only limited experimental evidence supporting this hypothesis exists (Vojdani 2020; Vojdani 2021). The delivery of the Spike gene by different vaccine delivery platforms may result in a different expression pattern of the S protein, thus potentially affecting parameters like levels, kinetics, location and/or post-translational modifications. There are also differences in the biosynthesis, structural features, and presentation of the S protein in current COVID-19 vaccines (Heinz 2021) that may be additionally related to myocarditis/pericarditis incidence.

Evidence Source(s) and Strength of Evidence:

Myocarditis and/or pericarditis have been reported as rare events following vaccination against smallpox, hepatitis B, tetanus, human papillomavirus, and viral influenza and have been documented for COVID-19 vaccines (Mei 2018; Su 2021). A systemic review and meta-analysis revealed higher incidence of myopericarditis following smallpox vaccination but no significant difference after influenza vaccinations compared to COVID-19 vaccination (Ling 2022).

Among COVID-19 vaccines, myocarditis and/or pericarditis has been observed with mRNA vaccines (Husby 2021; Karlstad 2022; Ling 2022; Patone 2022) with an incidence significantly higher in males versus females, in people younger than 30 years, and after a second dose (compared to first or third dose). Additionally, a recombinant adjuvanted protein-based COVID-19 vaccine has been associated with a disproportional myopericarditis induction (Macías Saint-Gerons 2023).

Events of myocarditis and pericarditis have been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and in the post-marketing setting. Real world evidence data of US claims data sources showed a high level of certainty of an increased risk of myocarditis and pericarditis for males aged 18 to 39 years within 28 days of vaccination with Ad26.COV2.S.

Myocarditis and pericarditis are ADRs described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of myocarditis and pericarditis from clinical trial and post-marketing experience is provided in Section 16.3.1.4, Myocarditis and Pericarditis of this PBRER.

Risk Factors and Risk Groups:

Myocarditis and pericarditis have been reported in association with SARS-CoV-2 infection. Historically, myocarditis and/or pericarditis have been reported as rare events following vaccination against smallpox, hepatitis B and viral influenza (Su 2021). Myocarditis and pericarditis have also been reported with other COVID-19 vaccines (including mRNA-based COVID-19 vaccines and a recombinant adjuvanted protein-based COVID-19 vaccine). Young males appear to be at highest risk, predominantly after receiving the second dose of COVID-19 vaccination. The disease course is self-limiting in a vast majority of cases: 95% of patients show a rapid resolution of symptoms and normalisation of cardiac biomarkers, electro- and echocardiographic findings within days (Klamer 2022).

Preventability:

The CCDS (Section Warnings and Precautions) states that healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis and that vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Impact on the Risk-Benefit Balance of the Product:

Myocarditis and/or pericarditis has been reported very rarely in clinical trials and the post-marketing setting following vaccination with Ad26.COV2.S. Based on current clinical trial and post-marketing data and the information in the CCDS, the identified risk of myocarditis and pericarditis does not change the existing established risk-benefit balance for Ad26.COV2.S.

Public Health Impact:

The occurrence of myocarditis and pericarditis is very rare following vaccination with Ad26.COV2.S. Epidemiologic analysis of real world data (RWD) sources such as electronic medical records and healthcare claims, showed that the risk of myocarditis and pericarditis following COVID-19 vaccination is lower than following natural SARS-CoV-2 infection (Patone 2022). Therefore, the public health impact is currently considered to be low.

Thrombocytopenia, including Immune Thrombocytopenia

Potential Mechanisms:

The mechanistic evidence for vaccine-derived thrombocytopenia is not very well understood. It is suspected to have a strong immune component such as immunostimulation causing alterations in cytokines that abrogate platelet production from megakaryocyte precursors and antigenic mimicry between virus and platelet antigens, giving rise to cross-reactive antiplatelet antibodies

(anti-IIb/IIIa) and/or activation of cytotoxic T cells that decrease platelet survival (Wise 2007). Similar to other autoimmune disorders, molecular mimicry with bacterial or viral proteins might be one reason for the pathogenesis of ITP (Marini 2019).

The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Grobbelaar 2021; Lei 2021; Perico 2022; Robles 2022; Zhang 2020; Zheng 2021), and is hypothesised to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

Recent mechanistic studies (non-clinical studies, and studies using clinical trial samples) conducted by the MAH to study the pathogenesis of (vaccine-induced) TTS with potential relevance to thrombocytopenia (including ITP), did not elucidate a clear MOA for thrombocytopenia (including ITP) following Ad26.COV2.S administration.

Evidence Source(s) and Strength of Evidence:

Cases of ITP with very low platelet levels (<20,000 per μL) have been reported very rarely after vaccination with Ad26.COV2.S, usually within the first 4 weeks after receiving Ad26.COV2.S. This included cases with bleeding and cases with fatal outcome. Some of these cases occurred in individuals with a history of ITP.

Immune thrombocytopenia is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of ITP from clinical trial and post-marketing experience is provided in Section 16.3.1.5, Thrombocytopenia, including Immune Thrombocytopenia of this PBRER.

Immune thrombocytopenia is a challenging diagnosis, with no unique identifying features when it occurs after vaccination. Unlike vaccine-induced thrombosis and thrombocytopenia, ITP is a diagnosis of exclusion. There is no specific test that confirms the diagnosis, and clinicians therefore rely on the lack of distinguishing features of other diseases (Pishko 2021).

Risk Factors and Risk Groups:

Limited data from post-marketing experience with Ad26.COV2.S, including literature, suggest that individuals with chronic or recurrent ITP may be at increased risk of developing ITP following vaccination with Ad26.COV2.S.

Preventability:

The CCDS (Section Warnings and Precautions) provides guidance to healthcare professionals to be alert to signs and symptoms of thrombocytopenia.

In addition, the CCDS (Section Warnings and Precautions) states that if an individual has a history of ITP, the risk of developing low platelet levels should be considered before vaccination, and platelet monitoring is recommended after vaccination.

Impact on the Risk-Benefit Balance of the Product:

Immune thrombocytopenia is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. ITP has been reported very rarely following vaccination with Ad26.COV2.S and adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Based on current clinical trial and post-marketing data and the information in the CCDS, the risk-benefit balance for the vaccine is considered to remain favourable for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of ITP events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

16.4.2. Characterisation of Important Potential Risks

Important potential risks that may be associated with the use of Ad26.COV2.S include:

Vaccine-associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)

Potential mechanisms of enhanced disease may include both T cell-mediated immune responses (a Th2-skewed immune response favouring immunopathology) and antibody-mediated immune responses (antibody responses with insufficient neutralising activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells) (Graham 2020).

Evidence Source(s) and Strength of Evidence:

Based on past experiences in the development of vaccines against RSV, Dengue virus, SARS-CoV, and MERS-CoV, there is a theoretical risk for VAED, including VAERD, for SARS-CoV-vaccines (Chin 1969; Fulginiti 1969; Kapikian 1969; Kim 1969; Su 2020; Agrawal 2016; Bolles 2011; Deming 2006; Honda-okubo 2015; Houser 2017). As COVID-19 clinical manifestations are not limited to respiratory symptoms, not only VAERD, but also the broader term VAED is being taken into account.

VAED/VAERD has not been described in association with Ad26.COV2.S and has not been confirmed from any other late phase clinical trial of other COVID-19 vaccines.

Studies in Ad26.COV2.S-immunised Syrian hamsters and NHP conducted by the Company have shown the absence of enhanced lung pathology, absence of increased viral load, and absence of

enhanced clinical signs of disease compared with controls after SARS-CoV-2 inoculation, even under conditions of suboptimal immunity allowing breakthrough infection (van der Lubbe 2021; He 2021). Together with induction of neutralising antibodies and a Th1-skewed immune response after Ad26.COV2.S dosing, these data suggest that the theoretical risk of VAERD and VAED for Ad26.COV2.S is low. These data were corroborated by the findings in clinical trials which have shown no indication of the presence of VAED, including VAERD.

Characterisation of the Risk:

An update on the number of cases of VAED/VAERD from clinical trial and post-marketing experience is provided in Section 16.3.2.1, Vaccine-associated Enhanced Disease, including Vaccine-associated Enhanced Respiratory Disease of this PBRER.

Risk Factors and Risk Groups:

It is postulated that the potential risk may be increased in individuals producing lower neutralising antibody titers or in those demonstrating waning immunity (Graham 2020; Munoz 2021).

Preventability:

An effective vaccine against COVID-19 that produces strong humoral and cellular immune responses with a clear Th1 bias is expected to mitigate the risk of VAED, including VAERD (Lambert 2020; Graham 2020). Such an immune profile is elicited by Ad26.COV2.S in clinical trials and non-clinical studies.

Impact on the Risk-Benefit Balance of the Product:

A confirmed risk of VAED, including VAERD could significantly impact the risk-benefit balance of Ad26.COV2.S. The risk will be further characterised through followup 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.

16.4.3. Description of Missing Information

Use During Pregnancy

Evidence source:

There is limited experience with the use of Ad26.COV2.S in pregnant women.

Animal data from the EF-PPND toxicity study with Ad26.COV2.S indicate no adverse effect of Ad26.COV2.S on reproductive performance, fertility, ovarian and uterine examinations, or parturition. In addition, there was no adverse effect of vaccination on foetal body weights, external, visceral and skeletal evaluations, or on postnatal development of the offspring.

Pregnancy at baseline was not an exclusion criterion in Trial COV2008, and Trial COV2004 is a trial in pregnant women. Up to the cut-off date of 24 February 2022, 23 women who were pregnant at baseline received at least 1 dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). Of the pregnancies reported in Trial COV2004 (n=22), 9 were still ongoing, 11 had a normal outcome, and 2 had an outcome of preterm neonate (1 without complications and 1 with complications). The pregnancy reported in Trial COV2008 had an outcome of premature without complications. No safety concerns have been identified in this population.

Any case of study vaccine exposure during pregnancy was included in the Company's global safety database when reported during the course of the trials. As of the cut-off date of 24 February 2023, 131 unique pregnancies were retrieved from Company-sponsored clinical trials post-baseline; 111 involved maternal exposure and 20 were partner pregnancies; all following Ad26.COV2.S administration. Overall, reported outcomes were live birth (n=53), spontaneous abortion (n=14, including 1 case of missed abortion due to Trisomy 21), elective abortion (n=4, 2 due to congenital anomalies: skeletal dysplasia and unspecified anomaly), intrauterine death, live birth with congenital anomaly (congenital tracheomalacia and ventricular septal defect) (n=2 each), ectopic pregnancy (n=1), and unknown (n=56). Of note, 1 participant reported a twin pregnancy during the trial (1 with an outcome of spontaneous abortion, 1 with an unknown outcome).

Up to the cut-off date of 24 February 2023, 731 unique cases reporting use in pregnancy were retrieved from post-marketing sources (including spontaneous and solicited primary and booster cases); 729 involved maternal exposure and 2 were partner pregnancies. Of these unique pregnancy cases, 233 cases reported 237 outcomes due to 4 twin pregnancies. One twin pregnancy resulted in a spontaneous abortion of one twin and a live birth without congenital anomaly of the other and are included in the following counts. The outcomes included live birth without congenital anomaly (n=146 [including 1 set of twins]), spontaneous abortion (n=64 [including 2 sets of twins]), live birth with congenital anomaly (n=16), ectopic pregnancy (n=5), blighted ovum (n=2), and 1 case each of still birth without congenital anomaly, still birth with congenital anomaly, maternal death, and intrauterine death. Of the 64 spontaneous abortion outcomes, there were 14 outcomes with exposure before conception, 26 outcomes with exposure during the first trimester of pregnancy, and for the remaining 24 outcomes timing of vaccine exposure was not reported.

Safety data with Ad26.COV2.S when administered within 3 months before pregnancy as well as during pregnancy have shown no safety concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes.

Anticipated risk/consequence of the missing information:

Based on the nonreplicating nature of the vaccine and on non-clinical and limited clinical and post-marketing data available to date, the safety profile of Ad26.COV2.S when used in pregnant women is not expected to differ from that in the general population, with no specific safety concerns for pregnant women or fetuses to date. Therefore, as stated in the CCDS (Section Pregnancy, Breastfeeding and Fertility), the administration of Ad26.COV2.S in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and foetus.

A Phase 2 trial (COV2004) and a post-authorisation pregnancy exposure registry (COV4005) are ongoing to assess the safety and immunogenicity of Ad26.COV2.S in pregnant women and their offspring.

An update on the number of cases from clinical trial and post-marketing experience in pregnancy is provided in Section 16.3.5.1, Use During Pregnancy of this PBRER.

Use in Breastfeeding Women

Evidence Source:

Breastfeeding women were excluded from all clinical trials, except from the Phase 2 trial COV2008 and the Phase 3 trials COV3001, COV3003, and COV3009. Up to the cut-off date of 24 February 2022, 718 women who were breastfeeding at baseline have received at least one dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). No safety concerns have been identified for breastfeeding women. However, safety data for their breastfed children is currently not available.

Up to the cut-off date of 24 February 2023, there have been 137 unique cases (post-marketing spontaneous or non-interventional cases) of exposure to Ad26.COV2.S via breastfeeding. No safety signals were identified.

It is not known whether the components of Ad26.COV2.S or the antibodies induced by Ad26.COV2.S are excreted in human milk. Human data are not available to assess the impact of Ad26.COV2.S on milk production or its effects on the breastfed child.

Anticipated risk/consequence of the missing information:

No effects on the breastfed child are anticipated considering results from animal and human studies with Ad26-based vaccines, showing limited dissemination of the vaccine and no replication of the vector following IM injection. In the event that a small quantity of Ad26.COV2.S would be (transiently) excreted via the milk, it would not be considered a risk to the breastfed child, specifically with regard to infections, as Ad26.COV2.S is replication-incompetent and does not encode a complete SARS-CoV-2 virus. Therefore, as stated in the CCDS (Section Pregnancy, Breastfeeding and Fertility), the administration of Ad26.COV2.S while breastfeeding should be considered when the potential benefits outweigh any potential risks to the mother and child.

A small subset of subjects within Trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk. Breastfeeding women were also allowed to participate in Trials COV2008, COV3001, COV3003, and COV3009 to characterise the safety profile of Ad26.COV2.S in this subpopulation. An update on the number of cases from clinical trial and post-marketing experience in use in breastfeeding women is provided in Section 16.3.5.2, Use in Breast Feeding Women of this PBRER.

Use in Immunocompromised Patients

Evidence source:

Patients with stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 (eg, stable/well-controlled HIV infection), or those receiving chronic low-dose (less than 20 mg of prednisone or equivalent) immunosuppressive therapy were included in Trials COV2008, COV3001, and COV3009.

The efficacy of Ad26.COV2.S may be lower in immunosuppressed individuals.

The final analysis results of the double-blind phase in trial COV3001 showed that, overall, the vaccine was efficacious against molecularly confirmed moderate to severe/critical COVID-19 with onset at least 14 days and 28 days after vaccination across demographic and baseline characteristics subgroups. An exception was noted for HIV-positive subjects (with a stable/well-controlled HIV infection) in which the VE was lower. Due to few COVID-19 cases in HIV-positive subjects, this conclusion should be interpreted with caution. No clinically relevant difference in the reactogenicity profile could be observed in HIV-infected versus HIV-negative subjects (COV3001 CSR 2021).

In the FAS of Trial COV3001, SAEs were reported in 8 (1.3%) out of 604 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 (COV3001 CSR 2021).

Based on the final analysis results of the double-blind phase in trial COV3009, no conclusion can currently be made about VE in HIV-infected subjects due to the limited number of HIV-positive subjects. In the FAS of trial COV3009, SAEs were reported in 3 (1.4%) out of 213 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 (COV3009 CSR 2021).

Of the 65,490 subjects in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 1,440 (2.2%) subjects had a stable/well-controlled HIV infection. subjects with other immunodeficiencies were included at low numbers.

Anticipated risk/consequence of the missing information:

Given the fact that Ad26.COV2.S is a replication-incompetent vaccine, the safety profile of Ad26.COV2.S when used in immunocompromised individuals is not expected to differ from that

in the general population. There were no specific safety concerns and no notable differences between HIV-infected and healthy subjects with regard to reporting frequency or severity of AEs at any timepoint from the 2 pivotal trials.

Use in immunocompromised patients will be further characterised in the post-authorisation safety studies COV4003 and COV4001 and effectiveness study COV4004.

An update on the number of cases from clinical trial and post-marketing experience in use in immunocompromised patients is provided in Section 16.3.5.3, Use in Immunocompromised Patients.

Use in Patients With Autoimmune or Inflammatory Disorders

Evidence source:

There is limited information on the safety of Ad26.COV2.S in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Subjects with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) were eligible for enrollment in Phase 3 trials COV3001 and COV3009 at the discretion of the investigator. Of the 21,898 subjects in the FAS of trial COV3001 who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 552 subjects had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of these 552 subjects, 5 (0.9%) reported an exacerbation (flare-up) of their pre-existing autoimmune disorder during the double-blind phase of the trial. Of the 15,708 subjects in the FAS of trial COV3009 who received at least 1 dose of Ad26.COV2.S ($5x10^{10}$ vp dose level), 458 subjects had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of these 458 subjects, 2 (0.4%) reported an exacerbation (flare-up) of their pre-existing autoimmune disorder, during the double-blind phase of the trial.

An update on the number of cases from clinical trial and post-marketing experience in patients with autoimmune or inflammatory disorders is provided in Section 16.3.5.4, Use in Patients with Autoimmune or Inflammatory Disorders of this PBRER.

Population in need of further characterisation:

Use in patients with autoimmune or inflammatory disorders will be further characterised in the post-authorisation safety studies COV4003 and COV4001.

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

Evidence source:

Frail individuals, especially those with multiple comorbidities that may compromise their immune response, are at an increased risk for severe COVID-19. In addition, the safety profile in this

subpopulation could vary from that seen in healthy adults. Increased age and comorbidities are the 2 major risk factors for frailty.

Of the 65,490 subjects in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 25,737 (39.3%) subjects had 1 or more comorbidities associated with an increased risk for severe COVID-19. Of these 25,737 subjects, 11,102 (43.1%) were aged ≥60 years, 6,378 (24.8%) were ≥65 years, and 1,216 (4.7%) were aged ≥75 years.

There is limited information on the safety of Ad26.COV2.S in frail patients with comorbidities that may compromise their immune response.

Following a protocol amendment for Trial COV3001 on 14 December 2020, calculation of a frailty index has been included to be applied to subjects enrolled. Of the 19,577 subjects in the Per Protocol set who received Ad26.COV2.S (5x1010 vp dose level), 6 (<0.1%) were defined as frail and 2,147 (11.0%) were defined as pre-frail. Of the 6 frail subjects, 5 (83.3%) were aged ≥60 years. Of the 2,147 pre-frail subjects, 1,338 (62.3%) were aged ≥60 years (COV3001 CSR 2021).

Population in need of further characterisation:

Safety data will be further collected in individuals who are frail due to age or debilitating disease in the post-authorisation safety studies COV4003 and COV4001, and through routine pharmacovigilance.

An update on the number of cases from clinical trial and post-marketing experience in use in frail patients is provided in Section 16.3.5.5, Use in Frail Patients With Comorbidities (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders).

Long-term Safety

Evidence source:

There are limited data available on the long-term safety of Ad26.COV2.S. Subjects in Trial COV3001 were followed for at least 2 years. No new safety concerns were identified. Note that due to several study limitations, no conclusions on group comparisons could be drawn.

Based on long-term safety data from other Ad26-based vaccines (at least 6 months up to 5 years post-vaccination in clinical trials), no long-term safety issues have been identified (Adenoviral Vaccine Safety Database V7.0 2022).

Population in need of further characterisation:

The long-term safety of Ad26.COV2.S is not fully known, however there are no known risks with a potentially late onset based on the available evidence with other Ad26-based vaccines.

Long-term safety data are being collected for at least 2 years in Trial COV3009 following administration of Ad26.COV2.S, and for up to 1 year in the post-authorisation safety studies COV4003 and COV4001.

Subjects of Trial COV3009 who initially received placebo were unblinded and offered a single dose of Ad26.COV2.S (crossover vaccination), since the vaccine has received an EUA in the US and conditional Marketing Authorisation in the European Union/EEA. All subjects have been encouraged to remain in the trial and will be followed for safety as originally planned up to 2 years from time of enrollment into study.

An update on the number of cases from clinical trial and post-marketing experience in use in long-term safety is provided in Section 16.3.5.7, Long-Term Safety.

Interaction With Other Vaccines

Evidence source:

As no interaction studies have been performed, there are no data to assess if concomitant administration of Ad26.COV2.S with other vaccines may affect the efficacy or safety of either vaccine.

Population in need of further characterisation:

All reports describing interactions of Ad26.COV2.S with other vaccines per national recommendations will be collected and analysed as per routine pharmacovigilance activities. A coadministration study of Ad26.COV2.S with seasonal influenza vaccine (Trial COV3005) was completed during the previous reporting interval of the PBRER (25 February 2023 to 24 February 2024). No additional safety concerns were identified following the coadministration of the 2 vaccines.

An update on the number of cases from clinical trial and post-marketing experience in cases with interaction with other vaccines is provided in Section 15.3, Use with Concomitant Vaccination of this PBRER.

16.5. Effectiveness of Risk Minimisation

No significant new information on the effectiveness or limitations of specific risk minimisation activities for the important identified risk or important potential risk has become available during the reporting interval for Ad26.COV2.S.

17. BENEFIT EVALUATION

As of 03 November 2024, there have been 776,798,873 confirmed cases of COVID-19 globally, including 7,074,400 deaths. As of 31 December 2023, over 13.64 billion vaccine doses have been administered (WHO 2024a). In Europe, as of 24 November 2024, there have been a total of 280,716,246 confirmed cases of COVID-19, and 2,277,964 cases of COVID-19 related deaths (WHO 2024a).

In the US, as of 24 November 2024, there have been a total of 103,436,829 confirmed cases of COVID-19 reported, and 1,208,476 cases of COVID-19 related deaths reported. (WHO 2024a).

Over the course of the SARS-CoV-2 pandemic, changes in SARS-CoV-2 Spike protein occurred. Some changes may affect the virus's properties, such as how easily it spreads, the associated

disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures. WHO (WHO 2021; CDC 2021a), in collaboration with partners, expert networks, national authorities, institutions and researchers have been monitoring and assessing the evolution of SARS-CoV-2 since January 2020.

From mid-2020, the emergence of variants in several countries, such as UK, RSA, Brazil, India, US, Peru, and Columbia that posed an increased risk to global public health prompted the characterisation of specific VOCs and VOIs to prioritise global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic. Previous VOCs include Alpha (B.1.1.7, earliest detection: UK), Beta (B.1.351, earliest detection: Republic of South Africa [RSA]), Delta (B.1.617.2, earliest detection: India), Gamma (P.1, earliest detection: Brazil) and Omicron parent lineage (B.1.1.529, earliest detection: South Africa). Previous VOIs include Eta (B. 1.525; earliest detection in several countries), Iota (B.1.526, earliest detection: US), Kappa (B. 1.617.1, earliest detection: India), Lambda (C.37, earliest detection: Peru), and Mu (B.1.621, earliest detection: Colombia). On 15 March 2023, WHO updated their COVID-19 variant tracking system with changes to the definitions of VOC and VOI, to add a new category (variant under monitoring; VUMs) to track Omicron sublineages (WHO 2023c). In addition to the Omicron sublineage XBB.1.16 being classified as a VOI on 17 April 2023, and the pango lineages EG.5, BA.2.86, and JN.1 being classified as VOIs on 09 August 2023, 21 November 2023, and 09 February 2024, respectively, a number of other Omicron sublineages are designated as VUMs as of 17 May 2023 (WHO 2023d).

The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their potential to increase transmission rates and/or cause more severe disease (increased hospitalisations or deaths), and because of the possibility that currently authorised/approved COVID-19 vaccines or otherwise in clinical development will provide reduced protection against these variants (CDC 2021a; Rambaut 2020; Tegally 2020).

17.1. Important Baseline Efficacy/Effectiveness Information

The efficacy, immunogenicity, and safety data from the pivotal, randomised, double-blind, placebo-controlled, Phase 3 COV3001 study in adults ≥18 years of age supported a favourable benefit-risk profile for Ad26.COV2.S in the proposed indication, ie, active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults ≥18 years of age. Key efficacy data from the primary analysis (cut-off date 22 January2021) are summarised below.

- The co-primary hypothesis testing was successful for both co-primary endpoints and, as such, the ability of a single dose of Ad26.COV2.S at 5×10^{10} vp to protect against moderate to severe/critical COVID-19 as early as 14 days after vaccination was demonstrated in adults ≥18 years of age, including adults ≥60 years of age. The VE (adjusted 95% CI) was 66.9% (59.03; 73.40) and 66.1% (55.01; 74.80) from at least 14 days and at least 28 days after vaccination, respectively.
- Higher VE was observed against severe/critical COVID-19. The VE (adjusted 95% CI) was 76.7% (54.56; 89.09) as of 14 days and 85.4% (54.15; 96.90) as of 28 days after vaccination. This high VE was observed consistently across age groups, countries and regions.

- VE against moderate to severe/critical COVID-19 and against severe/critical COVID-19 after a single dose of Ad26.COV2.S was observed across age groups, countries, and in subjects with and without comorbidities, with varying degrees of protection.
- Ad26.COV2.S was observed to have an impact on COVID-19 related hospitalisation (including intensive care unit admission, mechanical ventilation and extracorporeal membrane oxygenation) and COVID-19 associated death. As of 28 days after vaccination, 0 versus 16 COVID-19 related hospitalisations were observed in the Ad26.COV2.S group compared to placebo.

VE against all severe/critical COVID-19 in the US was 78.0% (33.13; 94.58) and 85.9% (-9.38; 99.69), 14 and 28 days after vaccination, respectively. In South Africa this was 73.1% (40.03; 89.36) and 81.7% (46.18; 95.42), respectively and in Brazil this was 81.9% (17.01; 98.05) and 87.6% (7.84; 99.72), respectively, indicating that the vaccine protected against known variants of COVID-19 circulating during the conduct of the study.

17.2. Newly Identified Information on Efficacy/Effectiveness

Although protection with a single dose of Ad26.COV2.S in adults ≥18 years of age, including in adults ≥60 years of age against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries/territories, regions, and emerging SARS-CoV-2 variants, including VOCs/VOIs, there was a trend towards a decreased protection against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the COV3001 study, and this potentially contributes to the observed decrease, although waning protection (including waning of immunity) of Ad26.COV2.S cannot be excluded.

Vaccine Efficacy Against Moderate to Severe/Critical COVID-19, Severe/Critical COVID-19 and COVID-19 related Hospitalisations/Deaths

Company-Sponsored Clinical Efficacy Studies

At the time of the final efficacy analysis of the double-blind phase of Study COV3001 (cut-off date 09 July 2021) evaluating efficacy of a single dose schedule, there was a trend towards a decreased protection against moderate to severe/critical COVID-19 compared to the primary analysis. The estimate of VE against moderate to severe/critical COVID-19 appears higher after boosting with a second dose of Ad26.COV2.S in Study COV3009 (cut-off date 25 June 2021) than observed with single dose vaccination (COV3001 and COV3009), indicating that a booster dose may be beneficial to increase VE against moderate to severe/critical COVID-19.

Study VAC31518COV3001

At the final analysis of the double-blind phase, VE (95% CI) of a single dose of Ad26.COV2.S against molecularly confirmed moderate to severe/critical COVID-19 was 56.3% (51.30; 60.84) at least 14 days after vaccination and was 52.9% (47.06; 58.08) at least 28 days after vaccination. Based on the final efficacy analysis of the double-blind phase of Study COV3001, VE (95% CI) against severe/critical COVID-19 was 73.3% (63.94; 80.49) when evaluated at least 14 days after vaccination and 74.6% (64.70; 82.06) when evaluated at least 28 days after vaccination. VE against

severe/critical COVID-19 was consistent across age groups, subjects without/with comorbidities, regions, countries and against SARS-CoV-2 variants with sufficient cases, including the Beta, Gamma VOCs and Lambda, Mu VOIs (as discussed below). VE estimates (adjusted 95% CI) in prevention of COVID-19 related medical intervention (including COVID-19 related hospitalisations linked to objective findings [judged by adjudication committee]) were 76.1% (56.86; 87.67) at least 14 days after vaccination and 75.6% (54.26; 88.00), at least 28 days after vaccination. Ad26.COV2.S also continued to protect against COVID-19 related deaths, with VE estimates (95% CI) of 84.5% (47.30; 97.06) and 82.8% (40.49; 96.77), respectively. All COVID-19- related deaths occurring in the Ad26.COV2.S group were at the time of the primary analysis and in older adults with comorbidities.

When considering the VE against SARS-CoV-2 variants including VOCs/VOIs observed in the study, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or CIs were wide. For the Delta VOC, which emerged late in the study (>5.5 months after vaccination), there were 21 (11 in Ad26.COV2.S group versus 10 in placebo) moderate to severe/critical COVID-19 cases of which 2 cases in each group were severe/critical, precluding meaningful conclusions on VE against this VOC. Similarly, for the Alpha VOC there were 2 versus 4 severe/critical cases in the Ad26.COV2.S group versus the placebo group, not allowing to draw meaningful conclusions for severe COVID-19 caused by this variant. Generally, there was continued protection against severe/critical COVID-19 for SARS-CoV-2 variants, including Beta, Gamma VOCs (64%, 78%), Lambda, Mu VOIs (68%, 80%).

Differences were observed in protection against moderate to severe/critical COVID-19 among the SARS-CoV-2 variants including VOCs/VOIs (range VE estimates 10%-70%). No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI] 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<36%). The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). These findings potentially contribute to the observed reduction in protection against moderate to severe/critical COVID-19 since the primary analysis, however waning protection cannot be excluded.

While the analyses of Delta cases from clinical studies remains inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta and Omicron VOC in a real world setting (Verani 2022; Acuti Martellucci 2022; Adams 2022; Gray 2022; Kissling 2021; Lewis 2022; Vokó 2022; Wright 2022; Yi 2022; Zheutlin 2022).

Overall, estimates from real world studies during periods of time when surveillance studies have indicated that Omicron/Omicron sub-variants were in circulation show that VE of both a single and booster dose of Ad26.COV2.S was moderate with indications of waning over time against COVID-19 infection and higher against hospitalisations and intensive care unit admissions, with a booster dose showing a marked increase in VE compared to a single dose (DeSantis 2023; Ito 2023; Kompaniyets 2022; Lin 2022).

Study VAC31518COV3009

Efficacy results from final analysis of the double-blind phase (ie, primary analysis with cut-off date of 25 June 2021) of ongoing Phase 3 Study VAC31518COV3009, in which an Ad26.COV2.S booster dose is administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increases. At the final analysis of the double-blind phase, VE (adjusted 95% CI) against moderate to severe/critical COVID-19 (primary endpoint) was 75.2% (54.55;87.30) when evaluated at least 14 days after second vaccination. VE against moderate to severe/critical COVID-19, when evaluated at least 14 days after boosting, was consistent among age groups as well as among subjects with and without comorbidities. Some regional differences in VE were observed: in the US, VE (95% CI) against moderate to severe/critical COVID-19 was 93.7% (58.45;99.85) while lower VE (60.0% to 68.8%) was observed in other regions, which was possibly driven by reduced VE against certain SARS-CoV-2 variants.

Final analysis results of variants with sufficient cases available for meaningful interpretations (Alpha [B.1.1.7] and Mu [B.1.621]) show that, after the first dose of Ad26.COV2.S, efficacy 14 days post-dose 1 (Day 15-Day 56) for these 2 variants was 73.2% [95% CI: 48.4; 87.1] and 38.6% [95% CI: -43.9; 75.1], respectively. After the second dose (≥71 days), efficacy for Alpha and Mu was 83.7% [95% CI: 43.8; 97.0] and 53.9% [95% CI: -48.0; 87.6], respectively. Statistically significant efficacy for Mu and Delta (4 and 3 Delta cases in the Ad26.COV2.S group and placebo group, respectively) was not demonstrated. There were no reference strain cases in either the Ad26.COV2.S or placebo group in the follow-up 14 days after the booster dose (≥71 days). Note that single dose VE estimates in study COV3009 from Day 15 to Day- 56 were similar to those observed in the primary analysis of COV3001 with a similar follow-up time, despite the fact that the studies were not conducted at the same time and in partially different locations.

Altogether, the totality of data from these clinical studies allows us to conclude that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some variants circulating during the conduct of these clinical studies.

Note that while the analyses of Delta cases from these clinical studies remains inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta and Omicron VOC in a real world setting (DeSantis 2023; Ito 2023; Kompaniyets 2023; Lin 2022; Lewis 2022).

Real World Evidence (Effectiveness) Studies

In addition to the clinical efficacy studies (COV3001, COV3009 and COV4004), the Company has conducted a review of the currently available RWE effectiveness data on Ad26.COV2.S. The review included Company-sponsored, collaborative, and publicly available RWE studies reporting on the vaccine effectiveness of Ad26.COV2.S and is summarised below.

Study VAC31518COV4002

Interim results (up to 183 days after vaccination; median follow-up of 129 days) are available from Study COV4002, which is an observational, longitudinal, post-authorisation study to assess the effectiveness of a single dose of Ad26.COV2.S (5×10^{10} vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US. HealthVerity COVID-19 data consists of longitudinal, de-identified patient-level RWD for approximately 160 million patient lives submitted by US providers of inpatient, outpatient, pharmacy, and laboratory services from 01 March 2021 to 30 April 2022 from open-source medical claims data aggregated by HealthVerity. Overall, the results of the interim analysis indicate that a single dose of Ad26.COV2.S protects against observed COVID-19 and COVID-19-related hospitalisation in the real world setting and that the VE observed in pivotal study COV3001 translates into clinical practice, with sustained effectiveness up to 183 days post-vaccination (median 129 days for observed COVID-19 and 130 days for COVID-19 related hospitalisation), including amid high Delta variant incidence and the initial emergence of the Omicron BA.1 and BA.2 subgroups.

Study VAC31518COV4004

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

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

Study VAC31518COV4019

The 6-month interim results from a Company-sponsored COV4019 study captured a study period spanning 20 October 2020 to 02 May 2022. During this study period, surveillance data indicated that Omicron strains BA.1, BA.2, BA.2.12.1, and BA.5 were in circulation. Overall, results indicated that both homologous and heterologous booster doses of Ad26.COV2.S were found to be an effective strategy in preventing COVID-19-related hospitalisation and medically attended COVID-19 for at least 6 months. In addition a booster dose of Ad26.COV2.S provides additional protection against COVID-19-related hospitalisation and medically attended COVID-19 in the real world setting compared to a single Ad26.COV2.S dose.

Studies VAC31518COV3012 (Sisonke [Together]) and VAC31518COV3021 (Sisonke 2)

Sisonke is a Phase 3b, open-label, implementation study of VE of Ad26.COV2.S in Health Care Workers (HCW) sponsored by the South African Medical Research Council in South Africa which

commenced on 17 February 2021 and ended on 17 May 2021 (Bekker 2021). This study focused on HCWs aged >18 years of age with SARS-CoV-2 test results collected by the National Institute for Communicable Diseases in the COVID-19 notifiable medical conditions sentinel surveillance system. While not explicitly deriving VE against infection and hospitalisation, differences were noted between the Beta and the Delta and Omicron breakthrough infection patterns in SISONKE HCWs, with Delta (60%) and Omicron (B.1.1.529, 67%) producing a higher proportion of breakthrough infections (BTI)-related hospitalisations in individuals between 31 to 54 years of age than Beta (51%) (Goga 2021; Goga 2022). A concomitant reduction was observed in the 55+ age group (46% during Beta, to 33% during Delta, and 19% during Omicron [p<0.001]). During Omicron, 91% hospitalised HCWs required general ward care, 6% high care and 3% intensive care. This was significantly different from 89% general ward care, 4% high care, and 7% intensive care during Delta and 78% general care, 7% high care and 16% intensive care during Beta (p<0.001). During Beta and Delta, 43% of hospitalised HCW needed supplementary oxygen and 7 to 8% needed ventilation, compared with 16% and 0.2% respectively during the Omicron period (p<0.001).

The SISONKE 2 study evaluated early VE against hospital admissions of a homologous Ad26.COV2.S boost 4 to 6 months after primary vaccination during the Omicron wave (15 November 2021 to 14 January 2022) in South Africa (Gray 2022). Vaccine effectiveness of the Ad26.COV2.S vaccine booster was estimated using a test negative design. Vaccine effectiveness (95%CI) against COVID-19 hospital admission was 55% (22% to 74%) when evaluated 0 to 13 days after the booster and increased to 74% (57% to 84%) and 72% (59% to 81%) when evaluated 14 to 27 days and 1 to 2 months after the booster, respectively. Vaccine effectiveness (95% CI) against intensive care unit admission or high care was 69% (26% to 87%) at 14 to 27 days and 82% (57% to 93%) at 1 to 2 months after the second dose.

Summary of Evidence from Additional Real world Studies

Results of additional RWE studies that report Ad26.COV2.S effectiveness have recently been reported. These studies investigated the RWE of Ad26.COV2.S for prevention of COVID-19, hospitalisation and death using electronic health records from multi-state health systems, networks, and hospitals. These studies focus on individuals who received single homologous and heterologous doses of the Ad26.COV2.S vaccine with comparison to control groups following local regulatory approval. Results were reported across different geographies, age categories, ambulatory, and inpatient care settings (DeSantis 2023; Ito 2023; Kompaniyets 2023; Lin 2022; Lewis 2022). Single dose Ad26.COV2.S VE against infection were reported to be lower during Omicron-emerging and Omicron-predominated periods. Vaccination remained more effective in preventing hospitalisation and death during the Omicron-emerging and Omicron-predominated periods. Vaccine effectiveness against COVID-19 infections and COVID-19-related hospitalisations were observed in fully vaccinated individuals who received a booster dose. Fully vaccinated individuals who received heterologous Ad26.COV2.S or mRNA booster vaccines showed an increase in VE compared with homologous dose Ad26.COV2.S or mRNA vaccines during the Omicron periods. Despite these limitations, results from many of the studies (Bekker 2021; Corchado-Garcia 2021; Moline 2021; de Gier 2021) are consistent with the vaccine effectiveness against VOCs seen with the single dose Ad26.COV2.S vaccine in COV4002.

Key Immunogenicity Data

Previously submitted results from studies COV1001, COV1002, COV2001, and COV3009 have shown that a homologous booster dose of Ad26.COV2.S (5×10^{10} vp), either 2 or 3 months after the first vaccination, induced an increase in humoral immune responses, which were durable up to at least 4 to 6 months after booster vaccination. These data are consistent with the homologous Ad26.COV2.S booster data from the Mix and Match Study DMID 21-0012, in which the booster was administered >12 weeks after primary vaccination. In addition, a homologous Ad26.COV2.S booster, administered 2 or 3 months after primary vaccination in adults ≥18 years of age, elicited cellular responses that persisted up to at least 6 months after boosting. These data further support the durability of the immune responses elicited by a homologous Ad26.COV2.S booster.

Study VAC31518COV2008

Study COV2008 is a randomised, double-blind, multicentre, Phase 2 study in adults ≥18 years of age in the US, in which a homologous Ad26.COV2.S booster was administered ≥6 months after primary vaccination in Cohort 1 or Ad26.COV2.S booster was administered ≥6 months after primary vaccination with 2 doses of BNT162b2 in Cohort 2.

Data from the primary analysis of COV2008 Cohort 1 have demonstrated NI of neutralising antibody titres and response rates against the reference strain and the Delta variant after Ad26.COV2.S homologous booster vaccination at ≥6 months, compared with primary vaccination with Ad26.COV2.S. An exploratory descriptive analysis showed that neutralising antibody titres and response rates against the Beta variant at Day 15 post-homologous booster are consistent with non-inferiority criteria compared to neutralising antibody titres and response rates at Day 29 after primary vaccination. Titres and response rates against the reference strain, Delta, and Beta variants post-homologous booster were generally maintained between Day 15 and Day 29. Considering that neutralising antibody titres correlate with VE (Khoury 2021; Fong 2022), this demonstration of NI links the immunogenicity data following the booster to the efficacy demonstrated in the randomised controlled study (COV3001) following the primary vaccination. In addition, non-powered descriptive analyses indicate that neutralising antibody titres following a homologous boost were superior compared to those following primary vaccination, in line with the higher efficacy estimates observed in the COV3009 efficacy study. These data are consistent with the previously submitted results from COV1001 Cohort 2a and confirm that a higher immune response was observed with an interval of at least 6 months between the primary vaccination and the booster.

In COV2008 Cohort 2, NI was also demonstrated against the reference strain and the Delta variant after Ad26.COV2.S heterologous booster vaccination at ≥6 months, compared with primary vaccination with Pfizer BNT162b2. Neutralising antibody GMTs and seropositivity rates were also significantly increased against the Beta variant. Titres and responder rates post heterologous booster increased substantially between Day 15 and Day 29 for the reference strain and the Beta and Delta variants, at all dose levels. These data are consistent with previously submitted interim data (binding and neutralising antibodies) on heterologous boosting with Ad26.COV2.S from the Mix and Match Study DMID 21-0012.

Neutralising antibody responses against the Omicron BA.1 variant were lower than those against the reference strain, Delta variant, and Beta variant after homologous (Cohort 1) or heterologous (Cohort 2) booster vaccination with Ad26.COV2.S at the 5×10^{10}vp dose level. However, the kinetics of the neutralising antibodies against the Omicron BA.1 variant were similar to neutralising antibodies against the other strains. By Day 29 post-homologous booster, neutralising antibody titres were maintained at Day 15 levels, while titres and responder rates post heterologous booster increased between Day 15 and Day 29. Non-powered descriptive analyses indicate that by Day 15, neutralising antibody titres and response rates against the Omicron BA.1 variant post-homologous booster at the 5×10^{10}vp dose level were superior to those observed post primary vaccination.

Heterologous boosting with Ad26.COV2.S was further supported by data from DMID 21-0012, COV-BOOST, RRH-001 and by data from the literature.

Non-Company-Sponsored Interventional Studies

Heterologous boosting with Ad26.COV2.S is further supported by additional results from Mix and Match Study DMID 21-0012 and Study COV-BOOST, in which a heterologous Ad26.COV2.S was administered following completion of primary vaccination with an mRNA or adenoviral vector-based COVID-19 vaccine and from Study RRH-001 in which a heterologous boost was administered after primary vaccination with an inactivated whole-virion COVID-19 vaccine. Overall, heterologous boosting with Ad26.COV2.S following any of the abovementioned primary vaccination regimens strongly increased neutralising and binding antibody responses as well as cellular responses, including against some SARS-CoV-2 variants (Beta, Delta, and Omicron BA.1).

Literature Review

Finally, homologous and heterologous boosting with Ad26.COV2.S are further supported by data from the literature (Mod5.3.5.4/Literature Summary Report/Systematic Literature Review of Immunogenicity Data Post-Homologous or Post Heterologous Boost With Janssen COVID-19 Vaccine or Other [mRNA] COVID-19 Vaccines; Tan 2022). Fully vaccinated individuals with one of the 3 priming regimens (Ad26.COV2.S, mRNA-1273, or BNT162b2), who received a boost with one of these 3 vaccines in any combination, showed an increase in neutralising/binding antibody and cellular responses to the SARS-CoV-2 reference strain and several variants including Beta, Delta, and Omicron BA.1 and BA.2, compared with pre-boost timepoint. Neutralising antibodies were boosted by all vaccine combinations, including against Omicron strains, with a modest boosting being seen with Ad26 homologous boosting. This translates into an increased vaccine effectiveness against COVID-19 related infections, hospitalisations, and deaths after Ad26.COV2.S boosting, including during the Omicron-emerging and Omicron-predominant periods.

17.3. Characterisation of Benefits

With the disease burden of COVID-19 remaining high, a COVID-19 vaccine that can easily be administered in a regimen that elicits long-term high protection against symptomatic COVID-19 is needed. Protection against severe/critical disease and in older/fragile age groups and other

populations at high risk will reduce the burden on health care systems by lowering COVID-19 related hospitalisations/deaths. Also, protection with a similar magnitude against existing and (newly) emerging SARS-CoV-2 variants, will be of high value to continue fighting.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

Medical Need

On 11 March 2020, the WHO characterised the COVID-19 outbreak as a pandemic. In response to the public health emergency, the EMA pandemic Task Force was formed from 31 March 2020.The Ad26.COV2.S prophylactic vaccine programme is an accelerated development programme that was designed specifically to address the COVID-19 pandemic. Despite the present availability of currently authorised vaccines, and the prevalence of natural infections, herd immunity has not yet been achieved, and travel from countries with a higher incidence of infection as well as the emergence of new variants means that the potential for new outbreaks is still a significant concern. The risk of outbreaks and emergence of new variants highlights the need to continue primary vaccination. A 1-dose regimen and favourable storage conditions are advantages conferred by the Ad26.COV2.S vaccine in protecting against COVID-19 disease caused by the SARS-CoV-2 virus, which are particularly important for immunising hard-to-reach populations.

Over the course of the SARS-CoV-2 pandemic, several new SARS-CoV-2 VOCs emerged in the UK (B.1.1.7 lineage [Alpha]), in Brazil (P.1 lineage [Gamma]), in the RSA (B.1.351 lineage [Beta], B.1.1.529 lineage [Omicron]), and in India (B.1.617 lineage [Delta]), and new VOIs (eg, B.1.427/B.1.429 lineage [CAL.20, Epsilon] in California) continue to emerge, which may spread globally. The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their potential to increase transmission rates and/or cause more severe disease (increased hospitalisations or deaths), and because of the possibility that currently authorised/approved COVID-19 vaccines or otherwise in clinical development will provide reduced protection against these variants (CDC 2021b; Rambaut 2020; Tegally 2020). For example, data suggest that the B.1.351 variant is not neutralised by some monoclonal antibodies directed to the SARS-CoV-2 S protein and is resistant to neutralisation by plasma from individuals previously infected with 'Wuhan-like' SARS-CoV-2 (Wibmer 2021), although data obtained to date suggest that the impact on neutralisation by convalescent and post-vaccination sera is minimal to moderate (CDC 2021c). As of 3 November 2024, there have been 776,798,873 confirmed cases of COVID-19 globally, including 7,074,400 deaths. As of 31 December 2023, over 13.64 billion vaccine doses have been administered (WHO 2024a). In Europe, as of 3 November 2024, there have been a total of 280,582,899 confirmed cases of COVID-19, and 2,277,078 cases of COVID-19 related deaths (WHO 2024a).

SARS-CoV-2 can cause widespread damage in different organ systems mediated by the host's immune response. Severity of illness can range from asymptomatic infection to severe multiorgan failure. The incubation period following exposure to SARS-CoV-2 has been estimated anywhere between 2 and 14 days and varies by VOCs. In a pooled analysis of 181 confirmed

COVID-19 cases from China the median incubation period was estimated to be 5.1 days (95% confidence interval, 4.5 to 5.8 days). Noteworthy, compared with earlier VOCs, shorter incubation periods have been documented in infections with Delta and Omicron variants, with a median incubation period of 4 days (Hernandez Acosta 2022).

COVID-19 is associated with a severe disease course in about 23% and mortality in about 6% of infected persons. Individuals with comorbidities and clinical features associated with severity should be monitored closely, and preventive efforts should especially target those with diabetes, malignancy, and immunosuppression (Li 2021). A recent epidemiological update by WHO reported that more than 200 countries around the world have reported SARS-Co-V-2 variants of concern of which the newer VOC, Omicron has been reported by 76 countries so far since first being reported in November 2021 (WHO 2023e; Genomic epidemiology of SARS-CoV-2 2023). However, the case fatality rate is affected by factors that include age, underlying pre-existing conditions, and severity of illness and significantly varies between countries (Cascella 2022). Therefore, while the understanding of the epidemiology and clinical spectrum of COVID-19 is still evolving, the disease burden continues mounting.

Main Existing Treatment and Prevention Options:

Despite the ever-growing number of available treatment options, an emphasis remains on disease prevention for global control of SARS-CoV-2. Since transmission of SARS-CoV-2 occurs primarily through respiratory secretions (droplets) and to a lesser extent via contact with contaminated surfaces, covering coughs and sneezes as well as social distancing (maintaining a distance of 1.5 m or 6 feet from others) can reduce the risk of transmission. Mouth and nose coverings, if properly pursued, may further reduce the spread of droplets from infectious individuals to others when social distancing is not possible. Furthermore, frequent handwashing and the use of hand sanitiser (>60% alcohol) are effective in reducing acquisition (CDC 2021d). Finally, frequent testing for SARS-CoV-2, contact tracing, and local quarantine measures have shown to be effective in reducing virus spread.

Prophylaxis

As of 01 December 2023, besides the Janssen COVID-19 vaccine, the following vaccines have received (conditional) marketing authorisation from EMA (EMA 2023) and/or from the UK MHRA (NHS 2023a): the mRNA-based BNT162b2 vaccine Comirnaty from Pfizer and BioNTech and adapted vaccines, the mRNA-1273 vaccine Spikevax from Moderna Inc and adapted vaccines, the ChAdOx1-S (recombinant) vaccine Vaxzevria from AstraZeneca, the (recombinant) vaccine Nuvaxovid from Novavax and adapted vaccine, the (recombinant) vaccine VidPrevtyn Beta from Sanofi Pasteur, and the (recombinant) vaccine Bimervax from Hipra Human Health.

As of 03 October 2023, the following vaccines have received EUA or full regulatory approval from the FDA: Spikevax and adapted vaccine (Moderna Inc.), Comirnaty and adapted vaccine (Pfizer and BioNTech), and Novavax COVID-19 vaccine and adapted vaccine (Novavax) (FDA 2023a).

As of 16 June 2023, besides the Janssen COVID-19 vaccine, the following vaccines have received WHO emergency use listing: Comirnaty and adapted vaccines (BioNTech), Vaxzevria (AstraZeneca), the ChAdOx1-S (recombinant) vaccine Covishield (Serum Institute of India), Spikevax (Moderna Inc), the inactivated COVID-19 (Vero Cell) vaccine (Beijing Institute of Biological Products), the inactivated COVID-19 (Vero Cell) vaccine CoronaVac (Sinovac Life Sciences), the whole-virion inactivated coronavirus vaccine Covaxin (Bharat Biotech International), the SARS-CoV-2 rS protein nanoparticle (recombinant) vaccine Covovax (Serum Institute of India), Nuvaxovid and adapted vaccine (Novavax), the Ad5-nCoV-S (recombinant) vaccine Convidecia (CanSino Biologics), and the recombinant protein subunit vaccine SKYCovione (SK Bioscience) (WHO 2023a). On 09 October 2023, the Bimervax vaccine (Hipra Human Health) obtained the prequalification status from WHO (WHO 2023b).

Therapeutics

As of 08 August 2022, the following treatments received (conditional) approval by the EMA for the treatment of COVID-19: remdesivir (Veklury), tixagevimab/cilgavimab (Evusheld), anakinra (Kineret), PF-07321332/ritonavir (Paxlovid), regdanvimab (Regkirona), tocilizumab (RoActemra), casirivimab/imdevimab (Ronapreve), and sotrovimab (Xevudy) (EMA 2023). In addition, EMA endorses the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation (EMA 2020b). The following COVID-19 treatments are approved for use in the UK for people with COVID-19 who are at the highest risk of becoming seriously ill: remdesivir (Veklury), nirmatrelvir/ritonavir (Paxlovid), sotrovimab (Xevudy), and molnupiravir (Lagevrio) (NHS 2023b).

As of 25 May 2023, remdesivir (Veklury), baricitinib (Olumiant), and tocilizumab (Actemra), and nirmatrelvir/ritonavir (Paxlovid) are the only drugs currently approved by FDA for the treatment of COVID-19 (FDA 2023b; FDA 2023c).

In addition, the following medical products have been granted EUA to treat COVID-19: the antiviral molnupiravir, the IL-1 receptor antagonist anakinra, the monoclonal anti-human complement factor C5a antibody vilobelimab, COVID-19 convalescent plasma. The following medical products had been granted EUA but are currently not authorised in any US region due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to the product: casirivimab plus imdevimab, tixagevimab plus cilgavimab, sotrovimab, and bebtelovimab (FDA 2023a; FDA 2023b; FDA 2023c).

Apart from the above drugs and biological products for the treatment of COVID-19, other medicinal products, including but not limited to sedative drugs, personal protective equipment, ventilators, and diagnostic tests, received EUA because of the urgent medical need caused by the COVID-19 pandemic (FDA 2023a).

The National Institute of Health issued COVID-19 treatment guidelines including recommendation strategies for the use of different therapeutics, for the management of patients with different severities of disease (COVID-19 Treatment Guidelines 2024).

18.2. Benefit-risk Analysis Evaluation

Key Benefits

The SARS-CoV-2 outbreak was declared a public health emergency of international concern in January 2020 and ended by WHO on 05 May 2023. The COVID-19 pandemic has already caused over 7 million deaths worldwide and continues to devastate lives. Effective and safe COVID-19 vaccines that can be easily administered are pivotal in ending this pandemic. Therefore, the MAH has evaluated efficacy, immunogenicity, and safety of a 1-dose primary and (homologous) booster COVID-19 vaccine, Ad26.COV2.S, in an ethnically and geographically diverse adult population.

Key Efficacy Data From Phase 3 Studies and RWE

Previously submitted results from single dose study COV3001 and homologous booster study COV3009 indicated that administration of a homologous booster 2 months after primary vaccination with Ad26.COV2.S increased the point estimates of VE against symptomatic and severe/critical COVID-19, including against SARS-CoV-2 variants with sufficient cases for analysis, based on a 1-month median follow-up after the booster vaccination. Efficacy data from these Phase 3 studies showed that vaccination with Ad26.COV2.S provided a level of protection against any SARS-CoV-2 infections (both symptomatic and asymptomatic infections combined), with higher VE point estimates after a homologous booster. Although VE (95% CI) against asymptomatic SARS-CoV-2 infections was generally low after single dose vaccination in COV3001 (28.9% [19.99; 36.78]), a country specific subgroup analysis for the US has shown a VE (95% CI) of 58.8% (44.69; 69.54) when evaluated at least 28 days after vaccination, confirming that VE always needs to be interpreted in view of emerging SARS CoV 2 variants, including VOCs/VOIs, with varying levels protection against these. Furthermore, in case of breakthrough infections, a reduction in severity, duration, and symptoms of COVID-19 and a reduction in viral load was observed, potentially reducing the risk of transmission. This shift to lower COVID-19 severity may additionally explain the generally low VE estimates against asymptomatic SARS-CoV-2 infections compared with the higher VE estimates against more severe COVID-19.

Data from SISONKE 2 and other RWE studies confirm the benefit of a homologous or heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, also during the Omicron-emerging and Omicron predominant periods. The final results from Janssen's multi-country TNCC study (VAC31518COV4004) with data collection through February 2023 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 severe acute respiratory infection (SARI) hospitalisations. This protection persisted for up to 6 months after vaccination. Final results (up to 12 months after vaccination; median follow-up ranging from 243 days to 268 days) for Study VAC31518COV4002, which is an observational longitudinal post authorisation study to assess the effectiveness of a single dose of Ad26.COV2.S (5×10^{10} vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US demonstrated effective and stable VE for the single-dose Ad26.COV2.S, based on month on month analysis and Kaplan Meier plots through the end of September 2022. Additionally, final results (with 12 months of follow-up time from the date of booster vaccination for an exposed individual and the corresponding date for the matched

individual in the referent group) for the Study VAC31518COV4019, demonstrated that both homologous and heterologous booster vaccines provided protection against COVID-19 related hospitalisations for up to 12 months.

Supporting Immunogenicity Data

Previously submitted results from studies COV1001, COV1002, COV2001, and COV3009 have shown that a homologous booster dose of Ad26.COV2.S (5×10^{10} vp), either 2 or 3 months after the first vaccination, induced an increase in humoral immune responses, which were durable up to at least 4 to 6 months after booster vaccination. These data are consistent with the homologous Ad26.COV2.S booster data from the Mix and Match Study DMID 21-0012, in which the booster was administered >12 weeks after primary vaccination. In addition, a homologous Ad26.COV2.S booster, administered 2 or 3 months after primary vaccination in adults ≥18 years of age, elicited cellular responses that persisted up to at least 6 months after boosting. These data further support the durability of the immune responses elicited by a homologous Ad26.COV2.S booster.

Data from the primary analysis of COV2008 Cohort 1 have demonstrated NI of neutralising antibody titres and response rates against the reference strain and the Delta variant after Ad26.COV2.S homologous booster vaccination at ≥6 months, compared with primary vaccination with Ad26.COV2.S. Neutralising antibody responses against the reference strain elicited by either homologous or heterologous booster vaccination were durable for 6 months to one year in the final analysis. Beta and Omicron BA.1 variant neutralising antibody titres were also increased after a homologous boost compared to pre-boost titres albeit lower than for the reference strain and Delta variant.

In COV2008 Cohort 2, NI was also demonstrated against the reference strain and the Delta variant after Ad26.COV2.S heterologous booster vaccination at ≥6 months compared with primary vaccination with Pfizer BNT162b2. Neutralising antibody responses against the Omicron BA.1 variant were lower than those against the reference strain, Delta variant, and Beta variant after homologous (Cohort 1) or heterologous (Cohort 2) booster vaccination with Ad26.COV2.S at the 5×10^{10}vp dose level. However, the kinetics of the neutralising antibodies against the Omicron BA.1 variant were similar to neutralising antibodies against the other strains. Immunogenicity data showed that neutralising antibody responses against Omicron sub-variants BA.2 and BA.5 can be boosted by a single booster dose of Ad26.COV2.S (as assessed by validated psVNAs.) Neutralising antibodies against these sub-variants up to 15 days post-boost showed comparable results vs. wild type virus.

In COV3005, immunological non-inferiority of concomitant administration of the Ad26.COV2.S vaccine and a standard-dose influenza vaccine versus administration of the standard-dose influenza vaccine alone was demonstrated for 3 of the 4 influenza vaccine strains studied (A/Cambodia [H3N2], B/Victoria [B/Victoria], and B/Phuket [B/Yamagata]). The study marginally failed to demonstrate non-inferiority for the HI titers of the A/Victoria (H1N1) strain (upper bound was slightly higher than 1.5 [ie, 1.53]). Although non-inferiority was not met for the H1N1 strain, seroconversion and seroprotection rates against the 4 influenza vaccine strains were comparable 28 days after concomitant administration of the Ad26.COV2.S and influenza vaccines and 28 days

after administration of the influenza vaccine alone in the standard-dose groups. Thus, the lower H1N1 HI titers with concomitant administration were considered as clinically not relevant. Non-inferiority of the binding antibody response against SARS-CoV-2 after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent standard-dose influenza vaccine versus the administration of Ad26.COV2.S vaccine administered alone was also demonstrated in COV3005.

Heterologous boosting with Ad26.COV2.S was further supported by data from DMID 21-0012, COV-BOOST, RRH-001 and by data from the literature.

Overall Assessment of Benefit

Ad26.COV2.S is efficacious, elicits a durable humoral and cellular immune response, has favourable storage conditions, and only requires administration of a single dose for primary immunisation, which simplifies deployment of the vaccine. Both antibody levels and VE increased after the administration of a homologous Ad26.COV2.S booster at least 2 months after primary vaccination, supporting the hypothesis that antibody levels correlate with protection. For the reference strain and Delta, Beta, and Omicron BA.1 variant, heterologous booster vaccination with Ad26.COV2.S elicited higher neutralising antibody titres than homologous booster vaccination at all dose levels evaluated. Homologous and heterologous booster vaccination with Ad26.COV2S at the 5×10^{10} vp level and as low as 1×10^{10} vp given ≥6 months after primary vaccination induced neutralising antibody levels that were observationally higher than those seen following a homologous booster at 2 months. Together, these data indicate that a heterologous booster at the 5×10^{10} vp dose level, but also potentially at lower dose levels, will result in levels of protection that are at least as high as for a homologous boost at least 2 months after primary vaccination.

Furthermore, published data from SISONKE 2 and other RWE studies confirm the benefit of a homologous or heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, also during the Omicron-emerging and Omicron-predominant periods.

Ad26.COV2.S was approved in the EU for use as a booster vaccine as it has been demonstrated to be effective for both homologous and heterologous booster vaccination. In low- and middle-income countries with high need for both primary and booster vaccination. Ad26.COV2.S was a valuable and relevant asset to address the COVID-19 pandemic.

Key Risks

The safety concerns from the current cRMP (version 8.0; dated 06 February 2024) are provided in Table 89.

Table 89: Safety Concerns at the end of the Reporting Interval

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Venous thromboembolism Myocarditis and pericarditis Thrombocytopenia, including immune thrombocytopenia

Table 89: Safety Concerns at the end of the Reporting Interval

Important Potential Risks	Vaccine-associated enhanced disease, including VAERD
Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety

Key: VAERD= Vaccine-associated enhanced respiratory disease

The safety concerns from the EU RMP (version 8.2, dated 12 July 2024) in place at the end of the renewal reporting interval are presented in Section 16.1.2, At the End of the Reporting interval.

Overall Assessment of Risk

The initial safety profile of Ad26.COV2.S vaccine was established at the time of the first authorisation based on safety data at the time of the primary analysis of Study COV3001, complemented by safety data from the then ongoing Phase 1, 2 and 3 studies. Since then, additional information became available through routine safety pharmacovigilance activities (such as signal detection) for which the results were reflected in updates of the cRMP, EU RMP, Summary Safety Reports, PBRERs, and amendments to the Product Information.

A single dose of Ad26.COV2.S has an acceptable safety and reactogenicity profile in adults ≥18 years of age, including adults ≥60 years of age. In general, lower reactogenicity was observed in older adults compared to younger adults. The most frequently reported solicited (local and systemic) AEs (collected up to 7 days after vaccination in the Safety Subset in COV3001) after a single dose of Ad26.COV2.S 5×10^{10} vp were vaccination site pain, fatigue, headache, and myalgia. Most AEs were of mild or moderate severity, were transient in nature, and generally resolved within 1 to 2 days post-vaccination.

The most frequently reported unsolicited AEs (collected up to 28 days after vaccination in the Safety Subset in COV3001) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs by PT, not recorded as solicited AEs, were Chills, Nasal congestion, Arthralgia, Cough, and Diarrhoea. Most were of mild or moderate severity, and most were considered not related to the study vaccine by the investigator. The overall frequency of SAEs was low and balanced between placebo and active groups.

The safety of a homologous Ad26.COV2.S booster dose has been evaluated in several clinical studies including Study COV3009 and Study COV2008. Overall, the solicited adverse reaction profile for the homologous booster dose was similar to that after the first dose and there were no new safety signals identified. The safety of a heterologous Ad26.COV2.S booster dose after primary vaccination with 2 doses of an mRNA COVID-19 vaccine has been evaluated in Study COV2008 and 2 independent studies (COV-BOOST and DMID 21-0012 studies). There were no new safety concerns identified; however, a trend towards an increase in frequency and severity of solicited local and systemic AEs after the heterologous booster dose was observed when compared

with the homologous booster dose of Ad26.COV2.S. The safety of a heterologous Ad26.COV2.S booster dose after primary vaccination with an adenoviral vector-based COVID-19 vaccine was also evaluated in the COV-BOOST study; no new safety concerns were identified.

Post-marketing experience with Ad26.COV2.S has demonstrated a similar safety profile to that observed in clinical trials. Serious ARs observed in the post-marketing experience including TTS, GBS, ITP, VTE, and myocarditis and pericarditis occurred very infrequently, are adequately monitored, and do not outweigh the significant benefits of vaccination with Ad26.COV2.S. The current post-authorisation exposure is insufficient to establish differences in the onset and severity of these very rare ARs between primary and booster usage of Ad26.COV2.S.

Integrated Benefit-Risk Evaluation Conclusions

Despite increasing numbers of vaccinated subjects, and the fact that since May 2023 the ongoing SARS-CoV-2 pandemic is no longer considered as a PHEIC (WHO 2023f), SARS-CoV-2 continues to circulate worldwide and remains a public health concern. The emergence of new virulent lineages has fuelled the need for highly effective preventive measures. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S demonstrated high efficacy against severe/critical disease caused by SARS-CoV2 and protection against hospitalisation and death in clinical trial settings. Analysis of spontaneous reports of vaccination failure did not show trends for lack of efficacy. Altogether, the totality of data supports that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some emerging variants. Data on booster usage (homologous or heterologous) suggests increased effectiveness in protecting against COVID-19 including some VOC, VOI.

Increasing experience based on spontaneous/solicited post-marketing reporting of AEs have led to the identification of SAEs/reactions such as TTS, GBS, ITP, and myocarditis/pericarditis. These risks occur very infrequently, are adequately monitored and do not outweigh the significant benefits of single dose vaccination with Ad26.COV2.S in controlling the global pandemic.

19. CONCLUSIONS AND ACTIONS

During the interval of this update, no previously unrecognised ADRs with Ad26.COV2.S have been identified. Consequently, there has been no change to the safety sections of the prescribing information or patient information. No further safety actions are warranted.

The Company has decided not to pursue further development of the vaccine, including adapting the vaccine against emerging variants and paediatric usage, considering the evolution of the SARS-CoV-2 pandemic and competitive landscape where access to a variety of COVID-19 vaccines exists. Therefore, the Company has voluntarily withdrawn the marketing authorisation for Ad26.COV2.S in the EU region on 09 August 2024 with all doses in the field expired as of 30 September 2024. Continuous routine PV activities for Ad26.COV2.S will be performed in accordance with applicable requirements in countries where market licenses remain active.

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