EMA/CHMP/766600/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the annual renewal of the conditional marketing authorisation

Procedure no.: EMEA/H/C/005737/R/0063

Invented name: JCOVDEN

Common name: COVID-19 vaccine (Ad26.COV2-S [recombinant])

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	17 Oct 2022	17 Oct 2022
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	15 Nov 2022	17 Nov 2022
☐	CHMP and PRAC members comments	21 Nov 2022	
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	24 Nov 2022	25 Nov 2022 + 09 Dec 2022
☐	PRAC endorsed relevant sections of the assessment report	01 Dec 2022	01 Dec 2022
☒	Opinion	15 Dec 2022	15 Dec 2022

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1. Background information on the annual renewal

The European Commission issued on 11 March 2021, a conditional marketing authorisation (MA) for JCOVDEN. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH Janssen-Cilag International N.V., submitted to the Agency on 9 September 2022 an application for renewal of the conditional MA for JCOVDEN. The expiry date of the MA is 11 March 2023.

The period covered by this annual renewal is 1 August 2021 to 31 July 2022. Final reports addressing the remaining quality SOBs were submitted in September and October 2022 and outcome of these assessments are considered in this AR (procedures EMEA/H/C/005737/II/0064 and MEA/H/C/005737/II/0067).

2. Specific Obligations

2.1. Specific Obligations adopted with the initial marketing authorisation

Table 1. Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
SOB1	In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.	15 August 2021
SOB2	In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data for active substance manufacturing site Biological E. Limited (India).	fulfilled
SOB3	In order to confirm the efficacy and safety of Ad26.COV2.S COVID-19 Vaccine, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	31 December 2023

The initial quality SOB included in the conditional marketing authorisation related to the remaining validation and comparability data for the finished product site Catalent Bloomington (US), has already been fulfilled previously (21 Oct 2021). Several variations which have been submitted post-approval of the conditional MA to implement additional manufacturing sites in the conditional MA and additional following quality-related specific obligations were included in Annex II as part of SOB1 (see Table 2). One new quality specific obligation on the active substance was introduced post-authorisation (SOB2). These active substance manufacturing sites were also conditionally approved via variation procedures with the specific obligation to provide additional validation and comparability data.

The following table provides a full overview of the current status of fulfilment for all specific obligations.

Table 2. Full overview of the current status of fulfilment for all specific obligations

Number	Description	Status
SOB1	In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data for the manufacturing sites:	
	- Catalent Bloomington (USA)	- fulfilled on 21 Oct 2021
	- Aspen (South Africa)	- fulfilled on 16 Dec 2021
	- IDK Biologika (Germay)	- fulfilled on 24 Jun 2021
	- Catalent Anagni (Italy)	- fulfilled on 16 Sep 2021
	- Merck Sharp & Dohme Corp, West Point (USA)	- fulfilled on 1 Sep 2022
	- Biological E Ltd., SEZ Unit (India)	- fulfilled on 1 Sep 2022
	- Sanofi Pasteur Marcy l'Etoile (France).	- fulfilled on 8 Dec 2022
SOB2	In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data manufacturing sites:	
	- Janssen Biologics DS site (Leiden, the Netherlands)	- fulfilled on 10 Feb 2022
	- Biological E. Limited (India).	- fulfilled on 8 Dec 2022
SOB3 (converted to MEA)	In order to confirm the efficacy and safety of Ad26.COV2.S COVID-19 Vaccine, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	Converted to a MEA Category 3 study in the RMP : 31 December 2023

Since the granting of the conditional MA (cMA), the MAH has submitted the following SOBs:

Quality-related SOBs

The initial SOB included in the conditional marketing authorisation of March 2021, which related to the remaining validation and comparability data for the Catalent Bloomington site (US), has already been fulfilled previously (21 Oct 2021).

The following quality-related specific obligations were included in Annex II as part of several variations which have been submitted post-approval of the conditional MA to implement additional manufacturing sites in the conditional MA: Aspen (South-Africa), IDT Biologika (Germany), Catalent Anagni (Italy), Sanofi Pasteur Marcy l'Etoile (France), Merck Sharp & Dohme West Point (US) and Biological E. Limited (India) for finished product manufacturing; upgraded facility at Janssen Biologics Leiden (Netherlands) and Biological E. Limited (India) for active substance manufacturing. These manufacturing sites were also conditionally approved via variation procedures with the specific obligation to provide additional validation and comparability data.

- SO1: In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.
- SO2: In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data.

For all of the above-mentioned sites, the MAH has provided the remaining validation and comparability data as requested in SOB1 and SOB2. The data have been assessed and were found acceptable. Accordingly, the specific obligations related to the variations to implement the finished product sites

Aspen (South-Africa), IDT Biologika (Germany), Catalent Anagni (Italy), Merck Sharp & Dohme West Point (US), Sanofi Pasteur Marcy l'Etoile (France) and Biological E. Limited (India) can be considered as fulfilled. Also, the specific obligation related to the variation to implement the upgraded active substance manufacturing site (upgraded facility) at Janssen Biologics Leiden (Netherlands) can be considered as fulfilled, as well as the specific obligation related to the variation to implement the active substance manufacturing site Biological E. Limited (India).

Taken together, whereas SOB1 and SOB2 relate to different manufacturing sites which were either proposed in the original conditional MA or post-approval of the conditional MA via variation procedures, all data submitted thus far as part of these SOB1 and SOB2 ["In order to confirm the consistency of the finished product manufacturing process (SOB1)) or active substance manufacturing process (SOB2), the applicant should provide additional validation and comparability data"] were found acceptable and confirm that the manufacturing process yields product of adequate and consistent quality that complies with its specifications, confirming the validated status of the process.

In conclusion, all quality-related SOBs have been adequately addressed and can be considered resolved.

Clinical SOB

The MAH anticipates that the clinical study VAC31518COV3001 can be completed by 31 Dec 2023.

Considering the vaccination of a large proportion of the control arm and the possibility for all participants to be administered with a booster vaccine (JCOVDEN, also referred to as Ad26.COV2.S or another approved COVID-19 vaccine) it is considered that the continued follow-up would no longer contribute in a significant way to the safety and efficacy profile of JCOVDEN. It is not expected that the remaining outstanding data from study VAC31518COV3001 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of the vaccine. The remaining clinical SOB may therefore be reclassified as Category 3 study in the RMP, with the final clinical study report (CSR) to be submitted at a later stage as supportive data.

2.2. Outstanding Specific Obligations – status report for period covered

All quality-related SOBs have been adequately addressed and can be considered resolved. There are no remaining quality-related SOBs.

The clinical SOB may be reclassified as Category 3 study in the RMP, with the final CSR to be submitted at a later stage as supportive data.

2.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

The initial SOB included in the conditional marketing authorisation of March 2021, which related to the remaining validation and comparability data for the Catalent Bloomington site (US), has already been fulfilled previously.

The specific obligations related to the variations to implement the finished product sites Aspen (South-Africa), IDT Biologika (Germany), Catalent Anagni (Italy), Merck Sharp & Dohme West Point (US), Sanofi Pasteur Marcy l'Etoile (France) and Biological E. Limited (India) can be considered as fulfilled. Also the specific obligation related to the variation to implement the upgraded active substance

manufacturing site (upgraded facility) at Janssen Biologics Leiden (Netherlands) can be considered as fulfilled, as well as the specific obligation related to the variation to implement the active substance manufacturing site Biological E. Limited (India). Thus, all quality-related SOBs have been adequately addressed and can be considered resolved.

The clinical SOB can be reclassified as a Category 3 study in the RMP with a final CSR to be submitted at a later stage as supportive data. The SOB can be considered fulfilled and can be deleted from the Annex II.

In conclusion, as part of this annual renewal the CHMP is of the opinion that the quality and clinical SOBs can therefore be deleted from Annex II.

3. Additional scientific data provided relevant for the assessment of the benefit/risk balance

3.1. Quality

At time of approval of the conditional MA, a list of 14 recommendations (REC) (post-authorisation measures, PAM) was included.
Apart from the SOBs, the applicant has also provided additional quality data related to the following RECs:

REC 30: validation data of the third process validation inoculum batch produced at Janssen Biologics B.V. (Leiden, NL).

REC 33: evaluate the sensitivity of Ad26.COV2.S FP when exposed to light stress, a study based on the ICH Q1B requirement should be performed. The samples should be tested for potency by QPA, turbidity by A350, radius by DLS and aggregation by AF4-MALS.

REC 37: results of the 6 month time point of the FP container leachables study.

REC 39: remaining PPQ data and tier 2 comparability data to confirm that the 700L scale process at GRAM (US) is appropriately validated and yields DP that is comparable to the DP from the registered DP sites.

All recommendations have been adequately addressed by the MAH, except for two Recommendations related to stability test results (to be provided when the stability studies have been finalised in 2024). However, based on the currently available stability data, it is deemed acceptable and sufficient if the MAH informs the Agency in case any Out-Of Specification (OOS) results are observed for the ongoing stability studies. As such, there are no remaining quality PAMs- recommendations.

3.2. Non-clinical

During the reporting period of this annual renewal application, final study results of non-clinical studies conducted to characterize the potential mechanism underlying vaccine associated thrombosis with thrombocytopenia syndrome (TTS), Thrombocytopenia, including immune thrombocytipenia (ITP) and/or Venous thromboembolism (VTE) have become available. The available nonclinical studies provided relevant data that can be used to put published data into perspective and/or possibly deprioritize some aspects of the proposed hypotheses or underlying mechanisms but the data do not

allow to conclude on a final pathogenesis mechanism of vaccine-induced TTS. This data was assessed in procedure EMEA/H/C/005737/II/047/G.

3.3. Clinical immunogenicity and efficacy

During the covering period of this annual renewal application, new efficacy and immunogenicity data relevant to the initially approved indication have emerged. The indication has also been extended to include a posology for the use of JCOVDEN as homologous booster or heterologous booster following completion of primary vaccination with a COVID-19 mRNA vaccine or an adenoviral vector-based COVID-19 vaccine.

Regulatory procedures are summarised below.

Regulatory procedures impacting the Summary of Products Characteristics (SmPC)

- EMEA/H/C/005737/II/0033: Addition of a booster posology (homologous and heterologous following vaccination with an mRNA COVID-19 vaccine) based on interim efficacy and immunogenicity results from different clinical studies including the two randomized, double blind, placebo-controlled Phase 3 studies VAC31518COV3001 and VAC31518COV3009; and interim results from the phase 1/2 study DMID 21-0012. In addition, the MAH took the opportunity to update the efficacy data for the primary vaccination schedule based on the end of the double-blind phase, which corresponds to the final analysis from study VAC31518COV3001.
- EMEA/H/C/005737/II/0053 – *Procedure was approved outside the annual renewal period*: Addition of heterologous booster posology following priming with another adenoviral vector-based vaccine based on literature evidence from the COV-BOOST study. Section 5.1 of the SmPC has also been updated to describe data from studies COV-BOOST and DMID 21-0012. The MAH took the opportunity to address some of the clinical RECs from conditional MA and Var II-033.

Regulatory procedures not impacting the SmPC

- PAM REC 052,053,054,066,067: The scope of this PAM is to provide Analysis of Vaccine Efficacy/Effectiveness (VE) of Ad26.COV2.S during the Delta Variant Period from VAC31518COV3001 and VAC31518COV3009 studies and Real-World Evidence (RWE) and to clarify/address some of the Clinical Recommendations from the Booster variation (Var II-33).
- PAM REC 055,056,057,058,059,060,061,062,063,064,065: The scope of this PAM is to clarify/address some of the Clinical Recommendations from the initial conditional MA.
- PAM MEA 09: The scope of this PAM is to provide the protocol for VAC31518COV4004, a Post-authorization, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe.
- PAM MEA 11: The scope of this PAM is to provide the protocol for VAC31518COV4002, An Observational Post-Authorization Study to Assess the Effectiveness of Ad26.COV2.S for Prevention of COVID-19 Using Real-World Data.
- PAM 069-070-071: The scope of this PAM is to evaluate Real-world effectiveness data with JCOVDEN

3.4. Clinical safety

The MAH submitted the Addendum to Clinical Overview (ACO), covering the period from 01 August 2021 to 31 July 2022.

Worldwide Marketing Authorisation Status

The international birth date for Ad26.COV2.S is 25 February 2021 based on initial MA in Bahrain. Ad26.COV2.S is authorised in 108 countries/territories and import licenses have been granted in 20 countries/territories worldwide. In addition, Ad26.COV2.S obtained Emergency Use Listing from the World Health Organization.

Significant Actions Taken in the Reporting Period for Safety Reasons

Table 3 provides a summary of significant actions taken for safety reasons during the annual renewal reporting period.

Table 3 Summary of significant actions taken for safety reasons during the reporting period.

Date	Country	Issue	Significant Action Taken
03 August 2021	EU	Thrombocytopenia as an important potential risk. Proposal made for studies aimed at further characterisation of TTS and/or thrombocytopenia. Addition of GBS as an important identified risk.	An updated EU RMP was submitted to EMA (EMEA/H/C/005737/II/0018).
25 August 2021	EU	PRAC feedback on June 2021 MSSR including the request to add dizziness and ITP as ADRs to the EUPI and to include a new Warning/Precaution for ITP.	Type II variation (EMEA/H/C/005737/II/0020) submitted to EMA adding dizziness and ITP as ADRs to the EUPI and including a new Warning/Precaution for ITP. HA submissions were made to other HA's in line with local requirements.
27 August 2021	US	Post-authorisation experience: lymphadenopathy, paraesthesia, hypoesthesia, tinnitus, diarrhoea, and vomiting. FDA revised warning for anxiety-related reactions and replaced with a warning for syncope and proposed syncope be added to the ADR section.	Factsheets updates were submitted for FDA review, regarding additions to the Post-authorisation experience to include lymphadenopathy, paraesthesia, hypoesthesia, tinnitus, diarrhoea, and vomiting. On 30 Aug 2021, FDA sent a concurrence letter in agreement to the updated factsheets.
27 August 2021	ZAF	SAHPRA requested for DHCPL for GBS.	MAH provided argumentation to SAHPRA, that a DHCPL for GBS is not warranted to which the Agency agreed.
06 September 2021 and 10 September 2021	EU	PRAC assessment report for the fifth pandemic safety update, post-opinion measure MEA 014.4, received on 02 Sep 2021, included a request for evaluation within a post-marketing follow-up measure related to VTE (MEA/032).	Procedure number: EMEA/H/C/5737/MEA/032 Submission of clinical study data from Studies VAC31518COV3001 and VAC31518COV3009, an in-depth discussion on the overall potential for a causal relationship between the Ad26.COV2.S and VTE. Oral explanation with PRAC on the MAH's position regarding a causal relationship, label, and RMP update was done on 28 Sep 2021. On 30 Sep 2021, the final PRAC assessment for MEA/032 was received, requesting a variation to include VTE in Sections 4.4 and 4.8 of the SmPC.
23 September 2021	BEL	During the iCTA evaluation of Study VAC31518COV3005 FAMHP asked for an age restriction for enrolling participants in this study according to national COVID-19 vaccine recommendations.	Submission of a country specific protocol amendment to comply with FAGG requirement (on 12 Oct 2022).
28 September 2021	EU	PRAC request to submit DHPC for ITP combined with DHPC for VTE.	Combined DHPC letter covering ITP/VTE was submitted to EMA and was endorsed on 30 Sep 2021. Following EMA approval, the DHPC was submitted to EMA regulated countries and disseminated in Oct 2021. In other countries/territories, DHPC/SSI notifications were made to the HA in line with local requirements.

29 September 2021	EU	MIS signal identified by EMA for all COVID-19 vaccines.	Submission of response to EMA (EMEA/H/C/005737/SDA/031). Based on data and literature review, there was insufficient evidence to conclude that MIS is causally associated with the use of Ad26.COV2.S. Therefore, no proposed revisions to EU RMP and EUPI.
05 October 2021	EU	As follow-up of MEA/032 procedure, a variation was submitted to include VTE in Section 4.4 and 4.8 of the SmPC.	Procedure number: EMA/H/C/5737/IB/0027. Submission of a SmPC update to include VTE in Section 4.4 and 4.8. A favourable notification was received from EMA on 08 Oct 2021. Submissions to other HA's were made in line with local requirements.
29 October 2021	EU	Request from EMA as an outcome of the follow-up measure related to VTE to reclassify VTE from an important potential risk to an important identified risk in the EU RMP.	Submission of Type II variation (procedure no EMEA/H/C/5737/II/0029) to EMA including an EU RMP update reclassifying VTE from an important potential risk to an important identified risk.
03 November 2021	CHE	HA request to submit label update regarding CLS, ITP, VTE, and dizziness.	Type II variation submitted to Swissmedic to update Swiss product information with text in the Warnings and Precaution section for CLS and ITP and including CLS and dizziness as ADRs. Company rationale for not including text in Warnings and Precautions for VTE and for not including ITP and VTE as ADRs was accepted by Swissmedic.
04 November 2021	ESP	AEMPS rejection of Study VAC31518COV3005, as booster dose with adenoviral vaccines was not recommended to subjects who received mRNA as their primary vaccination and a booster dose was not foreseen for the general population at that time.	Study not conducted in Spain.
24 November 2021	US	Warnings and Precaution for ITP.	Amendment to the factsheets to propose a warning and precaution for ITP
25 November 2021	EU	PRAC request in final assessment report August 2021 MSSR (procedure number MEA 014.5) to submit label update for TM. A minor update to Section 4.4 of the SmPC related to TTS was also requested.	Type II variation (procedure number EMEA/H/C/5737/II/0035) submitted to EMA to update Section 4.4 and 4.8 of the EUPI with information on TM. An update requested by EMA related to TTS was also included: These cases occurred within the first 3 weeks following vaccination, and mostly in individuals under 60 years of age. HA submissions in other countries/territories were made in line with local requirements.
30 November 2021	CHE	HA request: statement/analysis on the benefit-risk ratio in younger adults, particularly with regards to VTE, including risk minimisation measures.	Submission of response to Swissmedic request. Approved indication remained unchanged.
01 December 2021	EU	EMA request as part of ongoing procedure II/18 to include thrombocytopenia (incl. ITP) as an important identified risk in the EU RMP.	Updated version of the EU RMP submitted to EMA in the context of ongoing procedure II/18.
14 December 2021	US	Contraindication for TTS.	US factsheets were updated for contraindications, warnings, and precautions for TTS. In addition, the overall safety summary including SAEs and other EOIs was updated. Relevant updates were made to the recipient and caregivers' factsheet.
16 December 2021	EU	EMA request as part of procedure EMEA/H/C/005737/II/33 (update to the EUPI to introduce a booster dose) to include a contraindication for individuals who have experienced TTS following	An updated EUPI, including the requested contraindication, was submitted to EMA as part of procedure EMEA/H/C/005737/II/33. This variation was approved on 16 Dec 2021.

		vaccination with Ad26.COV2.S.	
03 January 2022	FRA	ANSM request (in the context of their review of protocol amendment 6) to further update the VAC31518COV3009 protocol with a statement that the Sponsor will instruct Investigators to discuss national vaccination recommendations with study participants and to issue a DIL and updated ICF reflecting the national recommendations in FRA.	Submission to ANSM of updated ICF, DIL, and commitment to update the protocol at the time of the next protocol amendment for the VAC31518COV3009 clinical trial. ANSM approval for protocol amendment 6 was received on 07 Jan 2022.
14 January 2022 and 24 February 2022	CAN	MHPD requested the inclusion of "Malaise" to the adverse reactions section as well as the inclusion of "Myocarditis, Pericarditis, TM, and Small vessel vasculitis with cutaneous manifestations" to the Post-market ARs section of the Product Monograph. Addition of these requests were initiated further to MHPD review of the eighth MSSR for Ad26.COV2.S covering the period of 01 Oct 2021 to 31 Oct 2021.	SNDS submitted to MHPD on 08 Feb 2022 for the addition "Malaise" and "TM" to the ARs section of the Product Monograph. Product Monograph to be updated on 01 March 2022 to include "Myocarditis, Pericarditis" to the Post-market ARs section and "TM" to the Warning and Precaution section.
25 Jan 2022	EGY	Receipt of a DHPC request regarding the risk of GBS	The draft DHPC was submitted to the HA on 15 Feb 2022.
02 Feb 2022	BRA	ANVISA has requested to add to local labelling the following ADRs: TM, facial paralysis, photophobia, and eye pain after evaluating RMP submitted.	Request accepted by the Company and local labelling has been updated accordingly.
04 Feb 2022	ZAF	The following HA Request was received on 21 Jan 2022; "All applicants of COVID-19 vaccines must submit an assessment on menstrual disorders reported with the use of their COVID-19 vaccine."	Response was submitted on 04 Feb 2022, referring to reviews presented in previous MSSRs, and routine PV continued after that as agreed with EMA. It was concluded that there is insufficient evidence to support an association between menstrual disorders or post-menopausal haemorrhage and the Ad26.COV2.S.
08 Feb 2022	EU	Final PRAC assessment report of the Oct 2021 MSSR (MEA 014.7) contained a request to update the EUPI regarding 'small vessel vasculitis with cutaneous manifestations.'	Company position on this request was included in the Bimonthly SSR (01 Nov 2021 to 15 Jan 2022) submission. The MAH provided justification on not adding 'small vessel vasculitis with cutaneous manifestations' in the EUPI.
10 Feb 2022	BEL	A conditional approval was received by the Belgian HA (FAMHP) for protocol amendment 15 for the VAC31518COV1001 study. The condition by FAMHP was to restrict the age for the booster doses in the trial according to national recommendations. A booster can only be administered to participants ≥65 years of age.	A country specific protocol amendment is being prepared to address the request by FAMHP. The request concerns also Study VAC31518COV3009. A DIL is prepared to be distributed at the sites to raise awareness among the Investigators. For the COV1001 the PA15 was submitted to FAGG on 07 March 2022 and approval received on 18 March 2022. For the VAC31518COV3009 the DIL was distributed 01 March 2022
17 Feb 2022	FRA	Publication of a pharmaco-epidemiology study based on French national databases suggesting a slightly increased risk for MI with Ad26.COV2.S within 3 weeks of first dose.	Recommendation by the French NITAG, on 17 Feb 2022, pending conclusion of EMA/PRAC on the EU PV data, to suspend the use of the Ad26.COV2.S, except for people at risk of severe form who have a contraindication to an mRNA vaccine
23 March 2022	UK (GBR)	Request from MHRA information to the Bimonthly SSR 01 Nov 2021 to 15 Jan 2022 concerning reports of TTS following a booster dose with Ad26.COV2.S	Response to RFI was submitted on 31 March 2022.
29 March 2022	EU	Completion of an additional PV activity mentioned in the EU RMP version 3.1 (approved on 13 Jan 2022 via procedure: EMEA/H/C/005737/II/0029) to the Agency.	On 29 March 2022, a grouping of Type II-variations (EMA/H/C/5737/II/0047/G) covering the final study reports of 5 nonclinical TTS characterisation studies regarding Ad26.COV2.S was submitted.

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

07 Jul 2022	JOR	EUA not renewed	Emergent as API manufacturer for Ad26.COV2.S is currently not considered to be compliant with GMP for the manufacture of this API.

Key: ADR=Adverse Drug Reaction; AEMPS=Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicines Agency); ANSM=National Security Agency of Medicines and Health Products (French); ANVISA=Agencia Nacional de Vigilancia Sanitaria (Brazilian Health Regulatory Agency; API=Active Pharmaceutical Ingredients; AR=Adverse Reaction; BEL=Belgium; BRA=Brazil; CAN=Canada; CHE=Switzerland; CLS=Capillary Leak Syndrome; COVID-19=Coronavirus Disease-2019; DHPC=Direct Healthcare Professional Communication; DHPCL=Dear Healthcare Provider Communication Letter; DIL=Dear Investigator Letter; EGY=Egypt; EMA=European Medicines Agency; EMEA=European Medicines Evaluation Agency; EOI=Event of Interest; ESI=Emerging Safety Issue; ESP=Spain; eSSI=Externally-identified Significant Safety Issue; EU=European Union; EUA=Emergency Use Authorisation; EUPI=European Union Package Insert; FAGG=Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (Belgium); FAMHP=Federal Agency for Medicines and Health Products (Belgium); FDA=Food and Drug Administration; FRA=France; GBS=Guillain-Barré Syndrome; GMP=Good Manufacturing Practice; HA=Health Authority; HCP=Health Care Professional; ICF=Informed Consent Form; iCTA=initial Clinical Trial Application; ITP=Immune Thrombocytopenia; JOR=Jordan; JPN=Japan; LoA=Letter of Acceptance; MAH=Market Authorisation Holder; MEA=Medicines Evaluation Agency; MHLW=Ministry of Health, Labour and Welfare (Japan); MHPD=Mental Health Provider Data Exchange; MHRA=Medicines and Healthcare Products Regulatory Agency (UK); MI=Myocardial Infarction; MIS=Multisystem Inflammatory Syndrome; mRNA=Messenger Ribonucleic Acid; MSSR=Monthly Summary Safety Report; NITAG=National Immunisation Technical Advisory Groups (France); PBRER=Periodic Benefit-risk Evaluation Report; PI=Package Insert/Product Information; PMDA=Pharmaceuticals and Medical Devices Agency; PRAC=Pharmacovigilance Risk Assessment Committee; PV=Pharmacovigilance; RCG=Recipients and Caregivers; RFI=Request for Information; RMP=Risk Management Plan; SAE=Serious Adverse Event; SAHPRA=South African Health Products Regulatory Authority; SmPC=Summary of Product Characteristic; SNDS=Supplemental New Drug Submission; SSI=Safety Signal Investigation; SSR=Safety Summary Report; TM=Transverse Myelitis; TTS=Thrombosis With Thrombocytopenia Syndrome; TUN=Tunisia; UK=United Kingdom; US=United States; VTE=Embolic and Thromboembolic events; ZAF=South Africa; SOC=System Organ Class.

Significant changes made to the Reference Information (RI)

The RI for Ad26.COV2.S, according to the initial MA application, is the EU SmPC.

The EU SmPC in effect at the start of the annual renewal reporting period was dated 30 July 2021 and the EU SmPC in effect at the end of the renewal reporting period was dated 14 July 2022. The EU SmPC for Ad26.COV2.S was updated 9 times (of which 5 included significant changes) between 01 August 2021 and up to the data lock date (DLD; 31 July 2022) of this renewal reporting period. Other changes in EU SmPC are administrative and chemistry, manufacturing, and controls related which are not listed in the *Table 4*. The MAH provides a listing of significant changes to the EU SmPC during the renewal reporting period in *Table 4*.

Table 4 Significant changes to the EU SmPC within the Renewal Reporting Period (01 August 2021 to 31 July 2022)

EU SmPC Effective Date	Significant Changes
03 September 2021	**Section 4.8** Undesirable effects - Addition of new ADRs under their respective SOC and frequency. Blood and Lymphatic System Disorders - Lymphadenopathy; Nervous System Disorders - Paraesthesia and Hypoaesthesia; Ear and Labyrinth Disorders - Tinnitus; Gastrointestinal Disorders - Diarrhoea, Vomiting.
01 October 2021	**Section 4.4** Special warnings and precautions for use - Included information on Immune thrombocytopenia. **Section 4.8** Undesirable effects - Addition of new ADRs dizziness, Immune thrombo-cytopenia.
11 October 2021	**Section 4.4** Special warnings and precautions for use - Included information on Venous thromboembolism. **Section 4.8** Undesirable effects - Addition of Venous thromboembolism.
16 December 2021	**Section 4.2** Posology and method of administration - Addition of booster dose (second dose) information (homologous and heterologous following vaccination with an mRNA COVID-19 vaccine). **Section 4.3** Contraindications - Addition of history of confirmed TTS following vaccination with any COVID-19 vaccine.

	Section 4.4 Special warnings and precautions for use - Cautionary warning to individuals who have experienced TTS following any COVID-19 vaccination not to receive Ad26.COV2.S (with a cross reference to Section 4.3). Addition of statement regarding risk of very rare events after a booster dose has not been characterised. **Section 4.8** Undesirable effects - Addition of information related to the booster vaccination. **Section 5.1** Pharmacodynamic properties - updated to include final analyses from VAC31518COV3001 study and data to support the booster posology (VAC31518COV3009 study and MixNMatch [independent study]).
14 January 2022	**Section 4.4** Special warnings and precautions for use: Addition of transverse myelitis warning. Amendment of the wording on TTS to reflect the observed balanced gender in the TTS cases reported through the post-marketing data. **Section 4.8** Undesirable effects: Addition of transverse myelitis with not known frequency under Nervous system disorder SOC.
18 May 2022	**Section 4.8**. Undesirable effects- Added "Cutaneous small vessel vasculitis as a not known ADR under vascular disorders."

Note: The Patient Leaflet was updated accordingly in line with the updates shown.
Key: ADR=Adverse Drug Reaction; COVID-19=Coronavirus Disease-2019; EU=European Union; mRNA=Messenger Ribonucleic Acid; SmPC=Summary of Product Characteristics; SOC=System Organ Class; TTS=Thrombosis with Thrombocytopenia Syndrome

Estimated Exposure and Use Patterns

Cumulative Subject Exposure in Clinical Trials

Overall, an estimated 82,129 healthy participants have been enrolled in the Ad26.COV2.S clinical programme, of which approximately 68,580 participants have received Ad26.COV2.S in the Company-sponsored interventional clinical trials.

Of these trials, Ad26.COV2.S exposure concerned 580 participants in Phase 1 trials,[1] 935 participants in a Phase 1/2a trial,[2] 1,582 participants in Phase 2 trials,[3] 537 participants in the Phase 2a trial,[4] 283 participants in a Phase 2/3 trial,[5] and over 64,663 participants in Phase 3 trials.[6]

Additionally, 16,142 participants were exposed to Ad26.COV2.S in the pre-approval access programs[7], and 751,906 participants were exposed to Ad26.COV2.S in the other studies[8].

To date, no Company-sponsored interventional clinical trial of Ad26.COV2.S was completed.

Cumulative Patient Exposure from Marketing Experience

Estimates of exposure are based on the number of delivered doses reported from LYNX Finance and administered doses reported from Centers for Disease Control and Prevention for the United States (US), European Centre for Disease Prevention and Control for European Economic Area (EEA)

1 Trials included: VAC31518COV1002, and VAC31518COV1003.
2 Trial included: VAC31518COV1001.
3 Trials included: VAC31518COV2004, and VAC31518COV2008.
4 Trial included: VAC31518COV2001.
5 Trial included: VAC31518COV3006.
6 Trials included: VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, and VAC31518COV3009.
7 Programs included: VAC31518COV4006 and VAC31518COV4007.
8 Studies included: COV-BOOST (VAC31518COV2009), VAC31518COV2012, VAC31518COV2016 (AUR1-8-341), VAC31518COV3012 (Sisonke [Together]), VAC31518COV3018, VAC31518COV3021 (Sisonke Boost Open-label Study), VAC31518COV4012, and DMID 21-0012.

countries/territories, Korea Disease Control and Prevention Agency for South Korea, Ministério da Saúde for Brazil, and National Department of Health 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.

Cumulative Exposure Estimates

Since launch, it is estimated that approximately, 474,199,850 doses of Ad26.COV2.S were distributed worldwide, corresponding to 52,615,064 estimated administered doses.

Homologous Ad26.COV2.S Booster Doses for Cumulative Period

A total of 2,928,890 homologous Ad26.COV2.S booster doses were administered in South Africa, South Korea, and in the US from launch until 31 July 2022.

Post-approval use in special populations

Where post-authorisation use of Ad26.COV2.S has occurred in special populations, available information regarding cumulative patient numbers exposed is provided as follows:

- Cumulatively, use of Ad26.COV2.S was identified in 960 cases of pregnancy/breastfeeding.
- Ad26.COV2.S is not authorised for use within the paediatric population, which is defined as individuals under the age of 18 years. Cumulatively, use of Ad26.COV2.S was identified in 631 cases.

Data in Summary Tabulations

Summary Tabulations from Post-marketing Sources

During the reporting period, 68,177 serious adverse events (AEs) and 141,570 nonserious ARs were received from spontaneous sources and 1,024 serious AEs were received from non-interventional post-marketing studies and other solicited sources.

From spontaneous sources, non-interventional post-marketing studies, and other solicited sources, the System Organ Class (SOCs) including the most frequently reported adverse events were:

- General Disorders and Administration Site Conditions (71,543 adverse events)
- Nervous System Disorders (32,105 adverse events)
- Musculoskeletal and Connective Tissue Disorders (21,365 adverse events)
- Infections and Infestations (15,580 adverse events)
- Investigations (12,106 adverse events)

Overall, most of the reported adverse events were non serious and attributed to recognised adverse drug reactions such as headache, injection site pain and fever. No new safety concern is identified in this data.

Summaries of Significant Safety Findings from Clinical Trials and Non-Interventional Studies

Summaries of Significant Safety Findings from Clinical Trials

Completed Clinical Trials

During the renewal reporting period, no Company-sponsored interventional clinical trial of Ad26.COV2.S was completed.

Ongoing Clinical Trials

During the renewal reporting period, 11 Company-sponsored interventional clinical trials of Ad26.COV2.S were ongoing. Of these 11 clinical trials, 1 clinical trial was relevant for the SOB (VAC31518COV3001), 4 clinical trials (VAC31518COV2004, VAC31518COV2008, VAC31518COV3005, and VAC31518COV3006) were initiated during the renewal reporting period. A brief summary and safety findings of all ongoing clinical trials are presented below. Furthermore, more detailed safety findings from three clinical trials are provided in this section, as these trials provide key safety data from the primary dose (VAC31518COV3001), the booster dose (VAC31518COV3009) and the homologous/heterologous booster (VAC31518COV2008)

- Trial VAC31518COV1001

This is a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged between 18 to and 55 years and older than 65 years in good health with or without stable underlying conditions, to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2-dose levels, administered as a single dose or 2-dose schedule, with a single booster vaccination administered in 1 cohort. According to MAH, no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV1002

This is a Phase 1, randomised, double-blind, placebo-controlled trial in healthy adults aged 20 to 55 years and older than 65 years in good health with or without stable underlying conditions in Japan to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 dose levels, administered IM as 2-dose schedule. According to MAH, no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV1003

This is a Phase 1, randomised, observer-blind, parallel-group trial to compare the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at a single dose of 5×10^{10} vp in 2 different volumes in healthy adults aged 18 to 65 years. According to MAH, no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV2001

This is a Phase 2a, randomised, double-blind, placebo-controlled, multicentre trial evaluating Ad26.COV2.S across a range of dose levels and vaccination intervals in healthy adults aged 18 to 55 years inclusive and adults in good or stable health aged 65 years or older and to evaluate single dose level of Ad26.COV2.S (2.5×10^{10} vp) in healthy adolescents aged 12 to 17 years inclusive. According to MAH, no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV2004

This is a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, immunogenicity, and pregnancy outcomes of Ad26.COV2.S in healthy pregnant (second and/or third trimester of pregnancy) participants aged ≥18 to ≤45 years. According to MAH, no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV2008

This is a Phase 2, randomised, double-blind, parallel, multicentre trial to evaluate the immunogenicity, reactogenicity, and safety of Ad26.COV2.S administered as a 1-dose booster vaccination regimen (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) in adults aged 18 years or older, who have previously received primary vaccination in Trial VAC31518COV3001 (Cohort 1: homologous booster) or who previously received primary vaccination with the Pfizer BNT162b2 vaccine (Cohort 2: heterologous booster).

*MAH Safety Summary (*cut-off date of 15 December 2021)

The results from the descriptive safety and reactogenicity analyses showed that booster vaccination with Ad26.COV2.S at the 5×10^{10} vp, 2.5×10^{10} vp, and 1×10^{10} vp dose levels had an acceptable safety and reactogenicity profile, with no safety issues identified. In general, a less reactogenicity was observed in the homologous boosting regimen compared to the heterologous boosting.

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

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

In conclusion, up to the cut-off date, the results from the descriptive safety and reactogenicity analyses showed that the booster vaccination with Ad26.COV2.S at the 5×10^{10}vp, 2.5×10^{10} vp, and 1×10^{10} vp dose levels had an acceptable safety and reactogenicity profile with no safety issues identified. In general, a less reactogenicity was observed after the homologous booster vaccination than the heterologous booster vaccination. Also, a lower reactogenicity was observed in older adults (aged ≥60 years) than in younger adults (aged ≥18 to 59 years).

According to MAH, no new safety concerns have been identified after an Ad26.COV2.S homologous/heterologous booster dose.

- Trial VAC31518COV3001

This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy, and safety trial in adults aged 18 to 60 years and ≥60 years. The efficacy, safety, and immunogenicity of Ad26.COV2.S will be evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. All participants who initially received placebo in the double-blind phase have been offered to receive a single dose of Ad26.COV2.S vaccine. Additionally, the open-label phase of the trial is extended to include an open-label booster vaccination with a single dose of Ad26.COV2.S at the Year 1 or booster visit.

MAH Safety Summary (cut-off date of 9 July 2021)

The final analysis of the double-blind phase of Trial VAC31518COV3001 until cut-off date, confirms the established safety profile of Ad26.COV2.S.

The single dose of Ad26.COV2.S at a dose level of 5×1010 vp has an acceptable safety and reactogenicity profile in adults aged 18 years of age and older, including adults aged 60 years and older. No significant safety issues were identified.

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

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

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

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

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

- Trial VAC31518COV3003

This is a Phase 3, randomised, double-blind trial to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults aged 18 to 55 years, inclusive. This trial consists of 2 parts: main trial and sub trial. In the main trial, the safety, reactogenicity, and immunogenicity of 1 dose (dose 1 of the 2-dose regimen) and 2 doses of Ad26.COV2.S will be evaluated. In the sub trial, additional adult participants aged 18 to 55 years will be enrolled (into study groups 1, 3, 5, and 6) to further characterise the innate, pro-inflammatory, and other relevant (e.g., pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to thrombosis with TTS events. According to MAH no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV3005

This is a Phase 3, randomised, double-blind, parallel, multicentre trial to evaluate safety, reactogenicity, and immunogenicity of Ad26.COV2.S co-administered with a seasonal quadrivalent (standard-dose or high-dose) influenza vaccine. A *standard-dose* influenza vaccine administered in participants aged between 18 and 64 years and *high-dose* influenza vaccine administered in participants aged 65 years of age and older compared to administration of each vaccine separately to explore whether Ad26.COV2.S and the influenza vaccines can be administered concomitantly. According to MAH, no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV3006

This is a Phase 2/3, randomised, observer-blind, pivotal, adaptive trial to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a 1- or 2-dose regimen (56-day interval) in healthy adolescents aged 12 to 17 years inclusive. According to MAH no significant safety findings were identified from this trial during the renewal reporting period.

- Trial VAC31518COV3009

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

MAH Safety Summary (cut-off date of 25 June 2021)

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

The 2-dose schedule of Ad26.COV2.S at a dose level of 5×1010 vp has an acceptable safety and reactogenicity profile in adults aged 18 years and older, including adults aged and 60 years older. No significant safety issues were identified. In general, a lower reactogenicity was observed in older adults compared to younger adults in this analysis.

Up to the cut-off date, 17 deaths were reported during the double-blind phase: 4 in the Ad26.COV2.S group and 13 in the placebo group.

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

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

Numerical imbalances that were observed in Trial VAC31518COV3001 for the AEs of interest (pulmonary embolism, deep vein thrombosis, and convulsions/seizures) were not observed.

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

According to MAH, no new safety concerns have been identified after an Ad26.COV2.S primary or booster dose in Trial VAC31518COV3009 and overall, no significant safety findings from ongoing clinical trials were identified during the annual renewal reporting period that had an impact on the conduct of clinical trials, or that had an impact on the benefit-risk balance of Ad26.COV2.S.

To summarise, during the renewal reporting period, 11 Company-sponsored interventional clinical trials of Ad26.COV2.S were ongoing from which 4 clinical trials (VAC31518COV2004, VAC31518COV2008, VAC31518COV3005, and VAC31518COV3006) were initiated during the renewal reporting period. It is agreed with the MAH that no significant safety findings from these trials were identified during the annual renewal reporting period that had an impact on the benefit-risk balance of Ad26.COV2.S.

Independent Data Monitoring Committee/Data Safety Monitoring Board

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

Summaries of Significant Safety Findings from Non-interventional Studies

Completed Non-interventional Studies

During the annual renewal reporting period no *non-interventional* studies of Ad26.COV2.S were completed.

Ongoing Non-interventional Studies

During the renewal reporting period, based on review of the data from non-interventional studies for Ad26.COV2.S, no new information with potential impact to the benefit-risk assessment has been identified.

Other Clinical Trials

Completed other Clinical Trials

During the renewal reporting period, no other clinical trials/studies of Ad26.COV2.S were completed.

Ongoing other Clinical Trials

During the renewal reporting period, 8 interventional clinical studies were ongoing. The summary and safety findings from these studies are presented below:

- Study COV-BOOST (VAC31518COV2009)

This is a Phase 2, randomised, multicentre study conducting in the UK to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2. The study will initially consist of several cohorts enrolled in 2 or 3 stages. At the time of DLP of this renewal, 2,878 participants were enrolled, of which 206 received Ad26.COV2.S. During the renewal reporting period, according to MAH no relevant safety information related to Ad26.COV2.S from this clinical study became available.

- Study VAC31518COV2012

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

and older in Study Part A and Part B. A total of 478 participants were recruited. Enrolment of groups are open-label allocation and assessor masked. At the time of DLD of this renewal, 478 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

- Study VAC31518COV2016 (AUR1-8-341)

This is a Phase 2a, randomised, observer-blind, multicentre trial of the safety and immunogenicity of COVID-19 vaccine strategies in human immunodeficiency virus (HIV)-infected and HIV-uninfected adults. A total of 750 evaluable HIV infected (660) and HIV-uninfected (90) adult participants meeting all entry criteria (all inclusion and no exclusion criteria) are aimed for enrolled in 3 treatment strategies in 3 participant groups dependent on prior vaccination with a single dose of JCOVDEN (Group 1), 2 doses of Comirnaty (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 renewal, 12 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

- Study VAC31518COV3012 (Sisonke [Together])

This is a Phase 3b, open-label, single-arm, multicentre, implementation study to monitor the effectiveness of the single dose of Ad26.COV2.S among healthcare workers (HCWs) at least 18 years of age as compared with the general unvaccinated population in South Africa. All HCWs who register on the National Vaccination Registry were eligible for enrolment. At the time of DLD of this renewal, 499,887 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

- Study VAC31518COV3018

This is a Phase 3, prospective, open-label clinical trial with one randomised arm to evaluate the response of a heterologous additional dose with the Janssen Ad26.CoV2.S vaccine to provide vaccine-induced immunity for immunocompromised kidney transplant patients after receiving 2 or more doses of the Pfizer or Moderna COVID-19 vaccine. At the time of the data lock point (DLP) of this renewal, 25 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

- Study VAC31518COV3021 (Sisonke Boost Open-label Study)

This is a Phase 3b, open-label, single-arm, multicentre, implementation study in Sisonke participants in South Africa at least 18 years of age. This study will be conducted by Sisonke (VAC31518COV3012) sites in collaboration with routine National Department of Health vaccination centres in South Africa. All Sisonke participants registered on the National Vaccination Registry were eligible for enrolment, if eligibility is met. At the time of DLD of this renewal, 250,878 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

- Study VAC31518COV4012

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

vaccines. At the time of DLD of this renewal, 270 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

- Study DMID 21-0012

This is a Phase 1/2, open-label study in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This study is designed to assess the safety, reactogenicity, and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of Emergency Use Authorisation-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson and Johnson). At the time of the DLD of this renewal, 150 participants received Ad26.COV2.S in this study. During the renewal reporting period, according to MAH no relevant safety information related to Ad26.COV2.S from this clinical study became available.

MAH Summary

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

To conclude, it is agreed with the MAH that no significant safety findings from other clinical trials/studies were identified during the annual renewal reporting period that had an impact on the benefit-risk balance of Ad26.COV2.S.

Medication Errors

No relevant information has been identified on patterns of medication errors, or potential medication errors, associated with use of Ad26.COV2.S during the renewal reporting period.

Signal and Risk Evaluation

Summary of Safety Concerns at the start of the Reporting Period

A summary of the important safety concerns in place at the start of the annual renewal reporting period (per EU RMP version 1.4, dated 12 March 2021) is included in *Table **5***.

Table 5 Important Identified Risks, Important Potential Risks, and Missing Information in the EU RMP at the start of the Annual Renewal Reporting Period (01 August 2021 to 31 July 2022)

Important Identified Risks	• Anaphylaxis
Important Potential Risks	• Vaccine-associated enhanced disease (VAED), including VAERD. • Venous thromboembolism
Missing Information	• Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in patients with autoimmune or inflammatory disorders • Use in frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) • Interaction with other vaccines • Long-term safety

Key: COPD=Chronic Obstructive Pulmonary Disease; EU=European Union; RMP=Risk Management Plan; VAED=Vaccine-associated Enhanced Disease; VAERD=Vaccine-associated Enhanced Respiratory Disease

Signals during the renewal period

Closed Signals

Closed and Refuted Signals

During the renewal reporting period, the following new signals have been identified, evaluated, closed, and refuted with no confirmed safety issues:

- Blindness
- Flare of autoimmune disorders
- Multisystem inflammatory syndrome
- Myocarditis and Pericarditis
- Neuralgic amyotrophy
- Rhabdomyolysis
- Transverse myelitis- encephalitis (including acute disseminated encephalomyelitis)
- Vasculitis

The following 3 signals were evaluated, closed, and refuted with no confirmed safety issues since the DLP pf the last PBRER (24 February 2022) up to the DLP of the renewal reporting period.

- Coronary artery disease, including myocardial infarction: all cases of coronary artery disease, including myocardial infarction were evaluated in PRAC PSUR assessment report (EMEA/H/C/PSUSA/00010916/202202; period covered by the PSUR: 24/08/2021 To: 24/02/2022) and has been assessed in previous SSRs. No new safety information was identified during the reporting period.
- Immunoglobulin A (IgA) nephropathy: the MAH has provided a summary of this new signal. It is anticipated that this signal will be further presented in the next PSUR.
- Severe cutaneous adverse reactions were evaluated in the PRAC PSUR assessment report (EMEA/H/C/PSUSA/00010916/202202; period covered by the PSUR: 24/08/2021 To: 24/02/2022). No new safety concern was detected. Nevertheless, an updated cumulative review should be presented with the next PSUR.

Closed Signals that are categorised as Important Identified Risks

During this renewal reporting period, the following signals have been closed and are categorised as important identified risks:

- Guillain-Barré syndrome (GBS): this signal was assessed by the PRAC (EMEA/H/C/005737/II/0012), leading to an update of sections 4.4 and 4.8 of the SmPC to add GBS as an ADR, with frequency very rare. In RMP version 2.5 (EMEA/H/C/005737/II/0018), GBS was included as an important identified risk. The signal closure is endorsed.
- Thrombocytopenia, Including Immune Thrombocytopenia (ITP): Immune thrombocytopenia (ITP) was assessed by the PRAC (EMEA/H/C/005737/II/0020), leading to an update of sections 4.4 and 4.8 of the SmPC to add a new warning on ITP, and to add ITP to the list of adverse drug reactions with frequencies not known based on the PRAC request from the post-authorisation measure

MEA/014.3 (4th MSSR covering the month of June 2021). In addition, a warning in section 4.4 of the SmPC was added. The closure of the signal is accepted. In the RMP (version 2.5, dated 01 December 2021), ITP is characterised as "Thrombocytopenia, including ITP" and is listed as an Important Identified Risk

- Venous thromboembolism (VTE): this signal was assessed by the PRAC, leading to an inclusion of VTE in the SmPC as ADR. The SmPC has been amended to list VTE as an ADR in section 4.8 and a warning text has been added section 4.4 (EMEA/H/C/005737/IB/0027). The signal closure is accepted. VTE has been re-classified as an Important Identified Risk in the EU-RMP version 3.1 (EMEA/H/C/005737/II/0029).

Closed Signals that are categorised as Important Potential Risks

There were no closed signals that were categorised as important potential risk.

Closed Signals that are Identified Risks Not Categorised as Important

During this renewal reporting period, the following signal has been closed and categorised as *Identified Risk* not categorised as *Important*:

- Capillary leak syndrome (CLS): CLS was asseed by the PRAC (EMEA/H/C/005737/II/0010), leading to an update of section 4.3 (contraindications in individuals with a history of CLS), 4.4 and 4.8 of the SmPC. In the Core RMP (version 4.0; dated 09 December 2021) CLS was removed as Important potential risk. The signal closure is accepted.

Closed Signals that are Potential Risks Not Categorised as Important

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

Closed Signals that are Categorised as an Adverse Drug Reaction

- Facial paralysis: PRAC concluded an assessment with a recommendation to update the sections 4.8 of the SmPC by adding facial paralysis (temporary facial drooping, usually one-sided), including Bell's palsy, as a side effect. Based on clinical trial data, this side effect was considered to be rare (EMEA/H/C/PSUSA/00010916/202202).
- Diarrhoea, paraesthesia, hypoesthesia, lymphadenopathy, vomiting and tinnitus were assessed by the PRAC (EMEA/H/C/005737/II/0014), leading to an update of section 4.8 of the SmPC in order to include diarrhoea and paraesthesia as ADRs with frequency uncommon; and hypoesthesia, lymphadenopathy, vomiting and tinnitus as ADRs with frequency rare, as requested by PRAC from post-authorisation measures MEA 014.2 and MEA 014.3 (3rd and 4th MSSR covering May 2021 and June 2021, respectively).
- Dizziness was assessed by the PRAC (EMEA/H/C/005737/II/0020), leading to an update of sections 4.4 and 4.8 of the SmPC to add dizziness to the list of adverse drug reactions with frequencies uncommon; based on the PRAC request from the post-authorisation measure MEA/014.3 (4th MSSR covering the month of June 2021).

Summary of Safety Concerns at the end of the Reporting Period

During the renewal reporting period, the summary of safety concerns was re-evaluated. The EU RMP in place at the end of the annual renewal reporting period was version 4.2, dated 07 July 2022. The

important identified risks, important potential risks, and missing information in this EU RMP are presented in *Table* ***6***.

During the reporting period, anaphylaxis was removed from the list of safety concerns following Procedure EMEA/H/C/PSUSA/00010916/202108, the risk is now considered an Adverse Reaction not meeting the criteria for safety concern. The SmPC lists anaphylaxis in section 4.4 (with the statement of appropriate medical treatment and supervision needed) and in section 4.8 (frequency unknown).

Table 6 Important Identified Risks, Important Potential Risks and Missing Information in the EU RMP at the End of the Annual Renewal Reporting Period (01 August 2021 to 31 July 2022)

Important Identified Risks	• Thrombosis with thrombocytopenia syndrome • Guillain-Barré syndrome • Thrombocytopenia, including immune thrombocytopenia • Venous thromboembolism
Important Potential Risks	• Vaccine-associated enhanced disease (VAED), including VAERD
Missing Information	• Use in pregnancy and while breastfeeding • Use in immunocompromised patients • Use in patients with autoimmune or inflammatory disorders • Use in frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) • Interaction with other vaccines • Long-term safety

Key: COPD=Chronic Obstructive Pulmonary Disease; EU=European Union; RMP=Risk Management Plan; VAED=Vaccine-associated Enhanced Disease; VAERD=Vaccine-associated Enhanced Respiratory Disease

Literature

A search of the scientific literature using various databases MEDLINE® Embase® was performed to capture information that had a potential impact on the benefit-risk of Ad26.COV2.S. The MAH informs that if they become aware of new safety/efficacy information from unpublished abstracts/manuscripts these would also be considered for evaluation and the findings will be discussed.

The MAH identified a total of 25 publications of interest: 18 product specific and 7 related to class effect. Most of these articles provide additional data to further characterise the safety concerns (e.g. thrombosis at unusual sites, exacerbation of immune thrombocytopenia, use in pregnancy and while breastfeeding, Use in patients with autoimmune or inflammatory disorders, use in patients with comorbidities). Other articles provided supportive information for the assessment of safety signals that have been discussed in the context of other procedures such as PSUR or SSR (e.g. tinnitus, small cell vasculitis, Bell's palsy, pericarditis and myocarditis).

Overall, from the literature provided by the MAH, no new safety issues were identified during the annual renewal reporting period that had an impact on the benefit-risk balance of Ad26.COV2.S.

3.1. Pharmacovigilance inspections

A listing of pharmacovigilance (PV) system inspections of the Company by Health Authorities (HA) during the annual renewal reporting period of this ACO, regardless of product, is included in *Table 7* .

During this reporting period, there was 1 product-specific pharmacovigilance (PV) inspection and had observations. This product-specific PV inspection observation had no impact on the benefit-risk balance

for Ad26.COV2.S.In addition, there were 4 general PV inspections with significant observations. None of the significant observations had a direct impact on the benefit-risk balance for Ad26.COV2.S.

Table 7 A Listing of Pharmacovigilance System Inspections conducted within the Company during the Period Covered by the Renewal

QA Activity Reference #	Inspection Status	Inspection Conduct Start Date	Inspection Conduct End Date	Inspection Report Issue Date	Inspecting Authority	Site Inspected	Type of Inspection	Product (if product specific) / or related sampled reports)	PV Significant Observation (Yes /No)	Open PV Significant Observation (Yes/No)	Cause of Inspection
Pharma PV System											
RDQA Health Authority Inspection 377568	Closed	13 Jul 2021	13 Jul 2021	19 Nov 2021	Ghana - Food and Drugs Authority	Johnson & Johnson Middle East LLC	Pharmacovigilance System Inspection	n/a	n/a	n/a	Routine Inspection
RDQA Health Authority Inspection 377585	Open	7 Sep 2021	10 Sep 2021	13 Oct 2021	United Kingdom - Medicines and Healthcare Products Regulatory Agency	Janssen Cilag United Kingdom	Pharmacovigilance System Inspection	n/a	Yes	Yes	Routine Inspection
RDQA Health Authority Inspection 377601	Closed	18 Nov 2021	18 Nov 2021	26 Nov 2021	Belgium - Pharmaceutical Inspectorate	Janssen Pharmaceuticals	Pharmacovigilance System Inspection	n/a	No	No	Routine Inspection
RDQA Health Authority Inspection 377552	Closed	2 Dec 2021	3 Dec 2021		Korea - Ministry of Food and Drugs Safety	Jan-Cil Korea	Pharmacovigilance System Inspection	n/a	No	No	Routine Inspection
RDQA Health Authority Inspection 377592	Open	6 Dec 2021	16 Dec 2021	24 Feb 2022	Belgium - Pharmaceutical Inspectorate		Pharmacovigilance System Inspection	n/a	Yes	No	For Cause
RDQA Health Authority Inspection 377595	Closed	19 Jan 2022	19 Jan 2022	27 Jan 2022	Japan - Pharmaceuticals and Medical Devices Agency	Janssen Pharmaceutical K.K.	Pharmacovigilance System Inspection	SIMPONI	No	No	Routine Inspection
RDQA Health Authority Inspection 377606	Open	24 Jan 2022	2 Feb 2022	10 Mar 2022	Canada - Health Canada		Pharmacovigilance System Inspection	n/a	Yes	No	Routine Inspection
RDQA Health Authority Inspection 377610	Open	7 Feb 2022	18 Feb 2022	2 Mar 2022	Rwanda - Rwanda Food and Drug Authority		Pharmacovigilance System Inspection	n/a	No	No	Routine Inspection
RDQA Health Authority Inspection 377623	Closed	22 Apr 2022	22 Apr 2022	30 May 2022	Japan - Pharmaceuticals and Medical Devices Agency	Janssen Pharmaceutical K.K.	Pharmacovigilance Inspection	XEPLION	No	No	Routine Inspection
RDQA Health Authority Inspection 377625	Open	12 Apr 2022	12 Apr 2022	26 Apr 2022	Lithuania – Ministry of Health		Pharmacovigilance Inspection	n/a	No	No	Routine Inspection
RDQA Health Authority Inspection 377633	Open	12-May-22	13-May-22	25 Jul 2022	Turkey - Ministry of Health		Pharmacovigilance Inspection	n/a	Yes	Yes	Routine Inspection
RDQA Health Authority Inspection 377645	Open	20-Jun-22	21-Jun-22	4-Jul-22	Indonesia - Indonesian National Agency of Food & Drug Control		Pharmacovigilance Inspection	n/a	No	No	Routine Inspection
RDQA Health Authority Inspection 377630	Closed	15-Jun-22	15-Jun-22	22-Jun-22	Japan - Pharmaceuticals and Medical Devices Agency	Janssen Pharmaceutical K.K.	Pharmacovigilance Inspection	bosentan	No	No	Routine Inspection
RDQA Health Authority Inspection 377638	Open	28-Jun-22	29-Jun-22		Brazil - Ministry of Health	Not Applicable	Pharmacovigilance Inspection	n/a	No	No	Routine Inspection
RDQA Health Authority Inspection 377627	Open	16-May-22	19-May-22		United Kingdom - Medicines and Healthcare Products Regulatory Agency		Pharmacovigilance Inspection	n/a	No	No	Routine Inspection

3.2. Discussion

The safety profile of the primary vaccination with Ad26.COV2.S in adults aged 18 years and older described in the current SmPC is based on a primary pooled analysis of clinical safety data from the double-blind phase of Phase 3 studies (VAC31518COV3001 and VAC31518COV3009) and of Phase 1 and Phase 2 clinical studies (VAC31518COV1001, VAC31518COV1002, VAC31518COV2001) with Ad26.COV2.S 5×10^{10} vp (18 November 2021) (procedure EMEA/H/C/005737/II/0060 approved after renewal reporting interval), and on post-marketing data which became available following the initial authorization of the vaccine (from launch up to 31 July 2022, it is estimated that over 52 million doses of Ad26.COV2.S were administered worldwide).

The safety profile of the booster dose has been assessed in procedure EMEA/H/C/005737/II/0053/G (approved after renewal reporting interval): homologous booster, and heterologous booster following completion of primary vaccination regimen with a mRNA COVID-19 vaccine or adenoviral vector-based COVID-19 vaccine.

The most recent clinical AdVac safety database report (V7.0, dated 1 July 2022) has been assessed in the PAM EMEA/H/C/005737/REC/019.1 (approved after renewal reporting interval). A total of 48,744 participants have been vaccinated with an Ad26-based vaccine in 42 clinical studies that have been integrated in the AdVac Safety Database V7 (cut-off date of 31 December 2021). They were mainly adults (47,944 adults) and from COVID-19 vaccine studies (39,623 adults: 21,898 in VAC31518COV3001 and 15,707 in VAC31518COV3009).

During the renewal reporting interval, changes in the known safety concerns or newly identified safety issues resulting in an update to the EU RMP for Ad26.COV2.S. are summarised in the table below:

Table 8 Summary of Changes in the Safety Concerns Resulting in an Update to the EU RMP During the Annual Renewal Reporting Period (01 August 2021 to 31 July 2022)

Version Number	Approval Date and Procedure	Change
2.2	Not approved; replaced by v2.3 EMEA/H/C/005737/II/0018	• Important identified risk 'Guillain-Barré syndrome' added as response to the PRAC Assessment Report (dated 22 July 2021) for procedure EMEA/H/C/005737/II/0012. • Important potential risk 'Thrombocytopenia' added as a response to the PRAC Assessment Report (dated 07 July 2021) for procedure EMEA/H/C/005737/II/0006/G. • Update of characterisation of the important identified risk 'Thrombosis with thrombocytopenia syndrome'.
2.3	Not approved; replaced by v2.5 EMEA/H/C/005737/II/0018	• Important identified risk "Immune thrombocytopenia" added. • Important potential risk "Thrombocytopenia"' revised to Thrombocytopenia (excluding immune thrombocytopenia and thrombosis with thrombocytopenia syndrome)".
3.1	13 January 2022 EMEA/H/C/005737/II/0029	EU RMP version 2.4 and 2.5 were replaced by version 3.1 • Important potential risk "Venous thromboembolism" reclassified to an important identified risk. • Update of characterisation of the important identified risk "Thrombosis with thrombocytopenia syndrome" to categorise TTS cases by PRAC requested case definition. • The important potential risk "Thrombocytopenia (excluding immune thrombocytopenia and thrombosis with thrombocytopenia syndrome)" is revised to "Thrombocytopenia, including immune thrombocytopenia)". In addition, this risk is reclassified to an important identified risk. The previous important identified risk 'Immune thrombocytopenia' is now included under 'Thrombocytopenia, including immune thrombocytopenia)'.
4.1	Not approved; replaced by v4.2 EMEA/H/C/005737/II/0048/G	• Removal of the important identified risk of "Anaphylaxis" (Procedure EMEA/H/C/PSUSA/00010916/202108).
4.2	07 July 2022 EMEA/H/C/005737/II/0048/G	To address the PRAC request for procedure EMEA/H/C/005737/II/0048/G received on 30 June 2022, changes related to nonclinical mechanistic studies that are being assessed separately in procedure EMEA/H/C/005737/II/0047/G were removed from the EU-RMP: • Removal of data from the nonclinical mechanistic studies in Module SII and Module SVII.3.1 that were added in EU-RMP v4.1. • Addition of a note in Part III.2 (and related sections) for nonclinical mechanistic studies that were completed on time but are being assessed separately in procedure EMEA/H/C/005737/II/0047/G and are still listed as additional pharmacovigilance activities.

Key: EU=European Union; EMEA=European Medicines Evaluation Agency; PRAC=Pharmacovigilance Risk Assessment Committee; RMP=Risk Management Plan; TTS=Thrombosis With Thrombocytopenia Syndrome

Overall, review of ongoing clinical trial data and post-marketing experience collected during the annual renewal period does not modify the positive benefit-risk profile of Ad26.COV2.S.

4. Risk management plan

The MAH has confirmed the current approved RMP (version 4.2 dated 07 July 2022) remains unchanged and applicable.

As described above, based on the data submitted with the renewal application, the CHMP is of the view that no changes to the summary of safety concerns listed in the RMP are warranted. The remaining clinical SOB may therefore be reclassified as category 3 study in the RMP, with the final CSRs to be submitted at a later stage as supportive data. Thus, as an outcome of the renewal procedure, the MAH is requested to submit an updated RMP at the next regulatory opportunity.

5. Changes to the Product Information

The Annexes I, II and III were amended to reflect the granting of a marketing authorisation not subject to Specific Obligations for JCOVDEN (see Attachment 1).

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, JCOVDEN is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Overall conclusions and benefit-risk balance

6.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

Quality-related SOBs

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

The initial SOB included in the conditional marketing authorisation of March 2021, which related to the remaining validation and comparability data for the Catalent Bloomington site (US), has already been fulfilled previously.

The following quality-related specific obligations were included in Annex II as part of several variations which have been submitted post-approval of the conditional MA to implement additional manufacturing sites in the conditional MA: Aspen (South-Africa), IDT Biologika (Germany), Catalent Anagni (Italy), Sanofi Pasteur Marcy l'Etoile (France), Merck Sharp & Dohme West Point (US) and Biological E. Limited (India) for finished product manufacturing; upgraded facility at Janssen Biologics Leiden (Netherlands), and Biological E. Limited (India) for active substance manufacturing. These manufacturing sites were also conditionally approved via variation procedures with the specific obligation to provide additional

validation and comparability data.

- SOB1: In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.
- SOB2: In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data.

For all of the above mentioned sites, the MAH has provided the remaining validation and comparability data as requested in SOB1 and SOB2. The data have been assessed and were found acceptable. Accordingly, the specific obligations related to the variations to implement the finished product sites Aspen (South-Africa), IDT Biologika (Germany), Catalent Anagni (Italy), Merck Sharp & Dohme West Point (US), Sanofi Pasteur Marcy l'Etoile (France) and Biological E. Limited (India) can be considered as fulfilled. Also the specific obligation related to the variation to implement the upgraded active substance manufacturing site (upgraded facility) at Janssen Biologics Leiden (Netherlands) can be considered as fulfilled, as well as the specific obligation related to the variation to implement the active substance manufacturing site Biological E. Limited (India).

In conclusion, all quality-related SOBs have been adequately addressed and can be considered resolved.

An overview of the conditions and specific obligations submitted since the granting of marketing authorisation to date is presented below. In addition, a type IA to remove the exemption for the EU testing activities has been approved on 30 July 2021.

Table 9. Full overview of the status of fulfilment for all quality specific obligations

Specific obligation	**Status**
SO1 (FP): In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.	
(from initial conditional MA): The MAH should provide the complete process validation/ process performance qualification (PPQ) data (including hold times) for the **Catalent Indiana site**. Information demonstrating proper validation of the proven acceptance ranges for the critical process parameters during PPQ should be provided. In addition, comparability data should be provided to confirm that the finished product (FP) from the Catalent Indiana site is comparable to the FP from the GRAM site. **A) One interim report with initial PPQ data and tier 1 comparability should be submitted by 31 March 2021** **B) a final report with all remaining PPQ results and tier 2 data should be submitted by 15 August 2021.**	**Fulfilled (SOB 002 in SIAMED)** **a) SOB/002: fulfilled on 24 Jun 2021.** **b) SOB 002.1: fulfilled (type II/17 opinion on 21 Oct 2021)**
From IB/001/G: The MAH should provide post-approval as part of a specific obligation the process validation data	**Fulfilled (SOB 017 in SIAMED)**

(including hold times) for the **Aspen site**. Information on a proper validation of the PARs for the CPPs during PPQ should be provided. In addition, also comparability data should be provided post-approval to confirm that DP from the Aspen site is comparable to the DP from the registered DP sites. The following 3 reports are expected: **a) A first report containing CoAs with the QC release results of the 2nd and 3rd PPQ batch. This report should be provided post-approval as soon as possible and in any case before these two batches are released to the market (by 19 April 2021).** **b) A second report with initial PPQ data and tier 1 comparability (by 31 May 2021).** **c) A final report with all remaining PPQ results and tier 2 data (by 30 September 2021).**	**a) SOB 0017: fulfilled on 20 May 2021** **b) SOB 0017.1: fulfilled 19 Aug 2021** **c) SOB 017.2: fulfilled (type II/0026/G conclusion on 16 Dec 2021)**
<u>From IB/002/G:</u> The MAH should provide post-approval as part of a specific obligation the following data for the **IDT Biologika** site to confirm the validated status of the manufacturing process. The following reports are expected: **a) A first report containing CoAs with the QC release results of the 2nd and 3rd PPQ batch. This report should be provided post-approval as soon as possible and in any case before these two batches are released to the market (by 27 April 2021).** **b) A final report with results for the CPPs (including hold times) and the IPCs (in-process controls) for the first 3 DP lots produced at the IDT Biologika site, as well as data demonstrating the DP homogeneity for 1 DP lot (by 31 May 2021).**	**Fulfilled (SOB 0021 in SIAMED)** **a) SOB 0021: fulfilled on 20 May 2021** **b) SOB 021.1: fulfilled (type II/05 conclusion on 24 Jun 2021**
<u>From IB/08:</u> The MAH should provide post-approval as part of a specific obligation **the process validation data (including hold times) for the Catalent Anagni site.** Information on a proper validation of the PARs for the CPPs during PPQ should be provided. In addition, also comparability data should be provided post-approval to confirm that DP from the Catalent Anagni site is comparable to the DP from the registered DP	**Fulfilled (SOB 025 in SIAMED)**

sites. The following 3 reports are expected: **a) A first report containing CoAs with the QC release results of the 3rd PPQ batch. (due date: 16/07/2021)** **a2) A first report containing CoAs with the QC release results of the pending PPQ batch. (due date: 30/09/2021)** **b) A second report with initial PPQ data and tier 1 comparability. (due date: 15/12/2021)** **c) A final report with all remaining PPQ results and tier 2 data. (due date: 31/3/2022)**	**A1) SOB 025: fulfilled: CoA of 3rd batch assessed in variation IB /0013. SOB 025 Closed in siamed on 16.8.21** **The due dates were amended in IB/0013** **A2) SOB 025.1: fulfilled on 16 Sept 21** **B) SOB 025.2: fulfilled on 24 Feb 2022** **C) SOB 025.3: fulfilled (type II-50 conclusion on 10 Jun 2022)**
From IB/25/G: The MAH should provide post-approval as part of a specific obligation the **process validation data (including hold times) for the Merck Sharp & Dohme Corp, West Point, USA site.** Information on a proper validation of the PARs for the CPPs during PPQ should be provided. In addition, also comparability data should be provided post-approval to confirm that DP from the MSD West Point site is comparable to the DP from the registered DP sites. The following reports are expected: **a) A first report with initial PPQ data and tier 1 comparability. (due date: 20/12/2021)** **b) A final report with all remaining PPQ results and tier 2 data. (due date: 31/05/2022)** -	**Fulfilled (SOB 035 in SIAMED)** **A) SOB 035: fulfilled on 24 Feb 2022** **B) SOB 035.1: fulfilled (type II/57 conclusion 1 Sep 2022)**
From IB/36: The MAH should provide post-approval as part of a specific obligation the process validation data (including hold times) for the **Sanofi Pasteur Marcy L'Etoile site**. Information on a proper validation of the PARs for the CPPs during PPQ should be provided. In addition, also comparability data should be provided post-approval to confirm that DP from the Sanofi Pasteur Marcy L'Etoile site is comparable to the DP from the registered DP sites. The following 3 reports are expected: **a) A first report containing CoAs with the QC release results of the 2nd and 3rd PPQ batch.**	**Fulfilled (SOB 36 in SIAMED)** **A) SOB 36 fulfilled on 22 Apr 2022**

This report should be provided post-approval as soon as possible and in any case before these two batches are released to the market. (due date: 31/01/2022) **b) A second report with initial PPQ data and tier 1 comparability. This report may be combined with the first report if all concerned data are available at the same time. (due date: 31/01/2022)** **c) A final report with all remaining PPQ results and tier 2 data. (due date: 30/09/2022)**	**B) SOB 36 fulfilled on 22 Apr 2022** **C) SOB 36.1: fulfilled (type II-64 conclusion on 8 Dec 2022)**
From IB/52/G : The MAH should provide post-approval as part of a specific obligation the remaining process validation data and the remaining Tier 2 comparability data for the **Biological E Ltd., SEZ Unit (India)** site to confirm that **DP** from Biological E Ltd., SEZ Unit (India) is comparable to the DP from the registered DP sites. The following report is expected: **A final report with all remaining PPQ results and tier 2 data. (Due date: 31st August 2022)**	**Fulfilled (SOB 068 in SIAMED)** **SOB 068: Fulfilled (type II/0058/G conclusion on 1 Sep 2022)**
SO2 (AS): In order to confirm the consistency of the ACTIVE SUBSTANCE manufacturing process, the MAH should provide additional comparability and validation data.	
From IB/11 The MAH should provide post-approval as part of a specific obligation the **process validation data for the Janssen Biologics DS site (Leiden, the Netherlands)** to confirm the validated status of the manufacturing process. Information on a proper validation of the PARs for the CPPs during PPQ should be provided. In addition, also comparability data should be provided post-approval to confirm that DS from the Janssen Biologics DS site (Leiden, the Netherlands) is comparable to the DS from the registered DS sites/processes. The following reports are expected: **a) A first report containing CoAs with the QC release results of the 2nd and 3rd PPQ batch (with RCA results pending). This report should be provided post-approval as soon as possible and in any case before DP lots formulated with these two DS batches are released to the market. This report should also include the RCA test result of the 1st DS PPQ lot. (by 3 August 2021)**	**Fulfilled (SOB 0026 in SIAMED)** **a) SOB 026: fulfilled on 16 Sep 2021**

b) A second interim report containing including RCA results for PPQ batches 2 and 3, complete PPQ data and tier 1 comparability data. (by 13 August 2021) **c) A final report with tier 2 comparability data. (by 30 November 2021)**	**b) SOB 26.1: fulfilled on 11 Nov 2021** **c) SOB 26.2: fulfilled (type II/37 conclusion on 10 Feb 2022)**
<u>From IB/55/G</u> The MAH should provide post-approval as part of a specific obligation the process validation data and the remaining Tier 2 comparability data for the **Biological E. Limited site** (Plot No. 1, Biotech Park, Phase II, Kolthur Village, Shameerpet, Medchal-Malkajgiri District, Hyderabad, Telangana-500078 India) to confirm that the **DS manufacturing process** at the BioE site is appropriately validated and that the DS from the BioE site is comparable to the DS from the registered DS sites. The following reports are expected: **a) A first report with the initial PPQ data for the DS manufacturing process at BioE, as soon as possible.** **b) A final report with the tier 2 comparability data and any remaining PPQ results. (due date 31st October 2022)**	**Fulfilled (SOB 072 in SIAMED)** **a) SOB 072: fulfilled on 13 Oct 2022)** **b) SOB 072.1: fulfilled (type II-67 concluded on 8 Dec 2022)**

Taken together, whereas SOB1 and SOB2 relate to different manufacturing sites which were either proposed in the original conditional MAA or post-approval of the conditional MA via variation procedures, all data submitted as part of these SOB1 and SOB2 ("In order to confirm the consistency of the finished product manufacturing process (SOB1) or active substance manufacturing process (SOB2), the applicant should provide additional validation and comparability data") were found acceptable and confirm that the manufacturing process yields product of adequate and consistent quality that complies with its specifications, confirming the validated status of the process.

<u>Clinical SOB</u>

Description	Procedural number	Status
Specific Obligation: In order to confirm the efficacy and safety of Ad26.COV2.S COVID-19 vaccine, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.		
<u>From initial cMA:</u> Submission of final CSR for VAC31518COV3001 by 31 December 2023	***N.A.***	***The SOB for COV3001 linked to the cMA needs to be fulfilled by 31 December 2023. Based on the current status of COV3001, the MAH anticipates that the date of 31 December 2023 for completion of this SOB is feasible.***

The MAH anticipates that the study VAC31518COV3001 can be completed by 31 Dec 2023. The clinical safety profile, as well as the efficacy of this product, is considered comprehensively characterised and supports a positive benefit-risk balance. It is not expected that the remaining outstanding data in the final CSR of VAC31518COV3001 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of JCOVDEN. The clinical SOB may therefore be reclassified as category 3 studies in the RMP and deleted from Annex II, with the final CSRs to be submitted at a later stage as supportive data.

Conversion of the Specific Obligations (SOBs) to Category 3 studies in the RMP (MEAs)

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a marketing authorisation not subject to specific obligations. The clinical SOB 003 is reclassified as category 3 study in the RMP with the final CSR to be submitted at a later stage as supportive data.

Number	Description	Status
MEA	In order to confirm the efficacy and safety of Ad26.COV2.S COVID-19 Vaccine, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	31 December 2023

6.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the benefit-risk of JCOVDEN in the approved indication(s).

The data collected as part of the specific obligations for JCOVDEN during the period covered by this annual renewal confirmed its positive benefit-risk balance in the approved indication.

Main clinical studies:

The main evidence of safety, efficacy and immunogenicity for the initial conditional MA originated from five studies. These included three Phase 1/2 studies evaluating the immunogenicity and safety of Ad26.COV2.S (COV1001, COV1002, and COV2001) and two large Phase 3 trials evaluating the efficacy, safety, and immunogenicity of Ad26.COV2.S. The efficacy trials VAC31518COV3001 and VAC31518COV3009 assessed respectively a single- and a two-dose schedule (two months apart) vs. placebo in adults.

Only efficacy data from VAC31518COV3001 (single-dose schedule) were available at conditional MA. At that time, data from the primary analysis (cut-off date 22 January 2021) have been submitted. Data from the final analysis of the double-blind phase (cut-off date 9 July 2021) were submitted in the booster EMEA/H/C/005737/II/33.

Efficacy and immunogenicity data from COV3009 were submitted in procedure EMEA/H/C/005737/II/33, and presented up to the end of the double-blind phase, which corresponds to the primary/final analysis (cut-off date 25 June 2021).

In the PAM procedure 053-067 and in EMEA/H/C/005737/II/53/G (which is approved outside the period covered by this annual renewal), updated sequencing data were provided for VAC31518COV3001 and VAC31518COV3009, as well as updated analyses of efficacy by variant, but still not based on complete genome sequencing data. Analyses based on complete genome sequencing data are still to be finalized.

Efficacy data for the Delta period (open label phase) were provided for both efficacy studies (PAM procedure 053-067).

Trial VAC31518COV3001 is a randomised, double-blind, placebo-controlled, Phase 3 study conducted in adults 18 years of age and older in the US, several Latin American countries (Argentina, Brazil, Chile, Peru, Mexico, Colombia), and South Africa. Participants were randomised in a 1:1 ratio to receive Ad26.COV2.S at a dose level of $5x10^{10}$ vp or placebo intramuscularly. A total of 43,783 randomised participants received Ad26.COV2.S (n=21,895) or a placebo (n=21,888).

Trial VAC31518COV3009 is a randomised, double-blind, placebo-controlled Phase 3 study conducted in adults 18 years of age and older, in Europe, South Africa, the US and Latin America and Asia. A total of 31,300 participants were randomised in a 1:1 ratio to receive Ad26.COV2.S ($5x10^{10}$ vp, n=15,708) as a two-dose schedule given 56 days apart or placebo (n=15,592) intramuscularly.

In both studies, participants who became eligible to receive an authorized/licensed COVID-19 vaccine according to local recommendation could request to be individually unblinded. In addition, shortly following EUA in the US (on February 27, 2021), participants were systematically unblinded and those who originally received placebo were offered a single dose of the vaccine. A large proportion of the participants also received (booster) vaccination with other authorized vaccines. Furthermore, after authorization of the use of Ad26.COV2.S as booster (20 October 2021 in the US, 16 December 2021 in the EU), a 1-dose booster vaccination with Ad26.COV2.S was offered to ongoing participants in study VAC31518COV3001 and to ongoing participants who received only a single vaccination with Ad26.COV2.S in VAC31518COV3009. This resulted in a short follow up time up in the blind phase of both studies. In addition, in VAC31518COV3009, a large proportion (about half) of the subjects did not receive their second dose yet when unblinding occurred and therefore were not included in the per protocol (PP) set.

Results from academic studies (DMID 21-0012, COV-BOOST) were supportive for the use of Ad26.COV2.S as homologous booster or as heterologous booster following completion of primary vaccination with an mRNA COVID-19 vaccine or an adenoviral vector-based COVID-19 vaccine

(EMEA/H/C/005737/II/33 and EMEA/H/C/005737/II/53/G, which is approved after the period covered by this annual renewal).

Favourable effects

Efficacy of a single dose:

The clinical trial VAC31518COV3001 assessed a single dose of Ad26.COV2.S in multiple countries. There was a high diversity of variants amongst cases, without a dominant variant. Efficacy against moderate/severe COVID-19 (onset >14 days after vaccination) was 67% (adjusted 95% CI: 59.0; 73.4) and 56% (95% CI: 51.3; 60.8) respectively over a 2 months (primary analysis, cut-off date 22 January 2021) and a 4 months (final analysis of the double-blind phase, cut-off date 9 July 2021) median follow-up (FU) period, in SARS-COV-2 seronegative individuals.

In participants 65 years of age and older, efficacy against moderate/severe COVID-19 (onset >14 days after vaccination) was 82% (95% CI: 63.9; 92.4) and 64% (95% CI: 48.9; 60.2) respectively over a 2 months and a 4 months median FU period.

Number of cases and efficacy estimates were consistent when using the US FDA Harmonized (CDC) COVID-19 case definition or when using the endpoint 'symptomatic COVID-19' cases which include cases classified as either mild, or moderate to severe/critical, supporting an indication against COVID-19 of any severity. For this reason, 'COVID-19' is used in the SmPC section 5.1 to describe the primary outcome of the study.

The cumulative incidence curves of molecularly confirmed moderate to severe/critical COVID-19 cases (Kaplan Meier) suggest that the onset of protection is around Day 14 post-vaccination.

Efficacy against severe disease was demonstrated. Of the 116 vs. 348 primary endpoint cases with an onset at least 14 days after vaccination in the vaccine vs. placebo group respectively, 14 (12%) vs. 60 (17%) were classified as severe/critical (further referred to as severe, also in the SmPC). The point estimate of VE against severe disease was 77% (adjusted 95% CI: 54.6; 89.1) and 73% (95% CI: 63.9; 80.5), over a median follow up of approximately 2 and 4 months respectively, in SARS-COV-2 seronegative subjects.

Of the 14 vs. 60 severe cases with onset at least 14 days after vaccination in the Ad26.COV2.S group vs. placebo group, 2 vs. 6 were hospitalised. Three died (all in the placebo group). Most of the remaining cases only fulfilled the oxygen saturation (SpO2) criterion for severe disease (SpO2<93%). For many cases this was based on self-measured abnormal oxygen saturation episodes (at home). All cases were adjudicated by an independent committee of clinical experts.

In the PP analysis set, 40% of the participants had at least one comorbidity, the most common being obesity (BMI ≥30 kg/m2, 28%), hypertension (10%) and type 2 diabetes mellitus (7.5%). Only participants with stable conditions were enrolled. Efficacy against molecularly confirmed moderate to severe/critical COVID-19 was observed both in participants with and without comorbidities.

Efficacy of a single dose by variants:

In VAC31518COV3001, efficacy against moderate/severe COVID-19 with onset at least 14 days after vaccination by variant was estimated based on sequencing data of approximately 90% of the cases. Efficacy against moderate/severe COVID-19 against the reference strain and the Alpha variant was good (point estimate approx. 70%). The efficacy point estimate was also good for the Zeta/P2 variant (point estimate approx. 65%). However, efficacy point estimates suggest very poor or lacking efficacy for other variants (Beta, Gamma, Mu, Lambda).

The limited data for the Delta variant also point to a signal of lack of efficacy (point estimate -6%, based on 11 vs 10 cases in the Ad26.COV2.S group vs the placebo group), which was confirmed by additional analyses for the period when the Delta variant was predominant (01 July to 21 September 2021, open label phase of VAC31518COV3001).

Efficacy against severe COVID-19 could be estimated for some variants and data suggest that efficacy is maintained with point estimates above 60% (for the variants for which sufficient data were available, i.e. reference, Beta, Gamma, Mu).

Immunogenicity:

Ad26.COV2.S elicits both humoral and cellular immune responses as early as 14 days after 1 dose of Ad26.COV2.S, in both young and older adults.

A homologous booster dose of Ad26.COV2.S, given at 2, 3 or 6 months post-primary vaccination, induces an increase in both neutralizing and binding antibodies (Ab) against the original strain and variants of concern, when compared to pre-boost values, both in young and older adults.

A heterologous boost by Ad26.COV2.S induces an increase in both neutralizing and binding Ab against the original strain and the Delta variant (binding Ab), when compared to pre-boost values in subjects vaccinated with two doses of an mRNA vaccine approximately 3 months before.

Uncertainties and limitations about favourable effects

Efficacy of a two-dose schedule:

The clinical trial VAC31518COV3009 assessed a 2-dose schedule given 56 days apart vs placebo in multiple countries. Alpha and Mu were the two dominant variants. Several important limitations have been identified in trial VAC31518COV3009. Given the huge discrepancy between the FAS and the PP (approximately half of the subjects were excluded from the PP set), the analysis cannot be considered as resulting from a randomized comparison. In addition, data from this trial raise concern with respect to awareness of treatment allocation. The very short FU period post-dose 2 in trial VAC31518COV3009 considerably limits the interpretation of the results.

Efficacy of two doses of Ad26.COV2.S administered two months apart was 75% (95% CI: 54.6; 87.3) against moderate/severe COVID-19 (onset >14 days post-dose 2) over a median FU period of 36 days. For severe COVID-19 cases, high efficacy (100.0%; 95% CI: 32.62; 100.00) was observed in VAC31518COV3009, but the number of events is very limited (0 vs. 8), and the lower limit of the 95% CI is very low.

Large regional differences in terms of efficacy were observed, possibly driven by certain SARS-CoV-2 variants. In the last analysis submitted (procedure PAM 053-067), analyses post-dose 2 were provided and were based on complete sequencing data for the blinded phase. However, post-dose 1 data are still incomplete. There are limited data by SARS-CoV-2 variants for the two-dose schedule. VE estimates (95% CI) against moderate to severe/critical COVID-19 were 84% (43.8; 97.0) and 54% (-48.0; 87.6) for the Alpha and for the Mu (B.1.621) variants, respectively. Efficacy could not be estimated for other variants in VAC31518COV3009, due to insufficient numbers. No efficacy data are available for the Delta (4 and 3 cases in the Ad26.COV2.S and in the placebo group respectively).

Efficacy as a (homologous or heterologous) booster:

There are no efficacy/effectiveness data on Ad26.COV2.S when used as a heterologous booster.

The efficacy of a second (homologous booster) dose was not studied as none of the trials was designed to make any direct comparison between a two-dose and a single-dose schedule.

Efficacy data are available for a single and for 2-dose schedule with 2 months interval from separate trials. The efficacy point estimate was numerically higher in VAC31518COV3009 assessing a 2-dose schedule compared to the point estimate in trial VAC31518COV3001 assessing a single dose, but CIs widely overlap. Comparison of data across the Phase 3 trials suggest that a second dose administered at 2 months might increase the level of efficacy against COVID-19, including for variants. However, due to several sources of uncertainty, no conclusion could be drawn on the clinical added value (and magnitude of) a booster (second) dose of Ad26.COV2.S vs. a single dose. Data suggests that the increment in terms of protection could be limited.

Efficacy against the Omicron variant:

Omicron was not circulating during the double-blind period of both trials, therefore there is no efficacy data for this variant.

Effectiveness data by variant:

Only limited real world effectiveness (RWE) data are available after the use of JCOVDEN as primary vaccination or boost during the Alpha, Delta and Omicron predominant periods. RWE during the Omicron period was evaluated in EMEA/H/C/005737/II/53/G, which is approved after the period covered by this annual renewal.

In the period when the Alpha variant was mainly circulating, vaccine effectiveness after one dose of Ad26.COV2.S was overall in line with vaccine efficacy against any variant in the pivotal trial VAC31518COV3001 at time of conditional MA with a 2 months follow-up period.

During the Delta period, effectiveness of Ad26.COV2.S against mild to severe COVID-19 was evaluated based on RWE data from a Company-sponsored study in the US (COV4002), a collaborative study in South-Africa (Sisonke) and published RWE studies throughout the world (US, Puerto Rico, South-Africa, The Netherlands, Spain, Austria and Germany). One dose of Ad26.COV2.S induces overall good protection against severe disease, including COVID-19 related hospitalisation, ICU admissions and death, similar to other/previously circulating variants. For asymptomatic infection or mild disease, protection of vaccination is overall low, but data of different studies are somewhat inconsistent.

Important to consider when interpreting the data is that VE against the VOC usually refers to VE during a period when that VOC was dominant or emerging, which implies that VE estimates obtained may also be affected by other circulating variants. Finally, many limitations related to RWE data are contributing to differences between study results, which should therefore be considered cautiously.

Duration of protection after a single dose:

Efficacy against symptomatic COVID-19 was assessed over a 4 months median FU period (data up to 6 months post-vaccination) in study VAC31518COV3001. A drop of efficacy was observed rapidly after a single dose (a few weeks following vaccination), in parallel with the progressive disappearance of the reference strain and emergence of several variants.

In contrast, no drop of efficacy against severe COVID-19 was observed at least up to 6 months following a single dose of Ad26.COV2.S. Efficacy was maintained despite the emergence of diverse variants.

Persistence of efficacy beyond 6 months after a single dose is not known, as efficacy data are not available after this timepoint.

Efficacy of a two-dose schedule was studied over a very short time of FU period of 36 days post-dose 2. No data will be available thereafter.

RWE data are currently insufficient to conclude about the duration of protection and potential waning of effectiveness after one or two doses of Ad26.COV2.S, as long-term VE data are lacking. However, RWE suggest that waning of protection from hospitalised disease seems to be limited up to approximately 6-7 months after vaccination with a single dose of Ad26.COV2.S.

Immunogenicity:

No immunological correlate of protection has been established.

Neutralizing and binding Ab levels after one vaccination with Ad26.COV2.S appear to be sustained up to at least 6 months. There is no clear decrease over time. A minor, and not systematic, trend for decreased Ab levels is observed at the later timepoints (6 or 8-9 months post-vaccination) when compared to earlier timepoints (1 or 2 months post-vaccination).

The humoral immune responses elicited by a booster dose was only investigated before immunogenicity started to wane (i.e. ≤6 months post-dose 1).

Results are from different studies, always with limited sample size. There are no nAb data from study VAC31518COV3009.

Most of the results are for the original Victoria strain. Limited data are available for the VOC. nAb levels against the variants are overall lower than for the parental strain.

There are no Ab data for the Delta variant when the second dose is given at 2 months post-dose 1. Data obtained when the second dose is given with a 6 month-interval still should be confirmed.

Data over a FU period of more than 1 month post-dose 2 are limited. A 2-fold decline of Ab titers is observed at 4-6 months post-dose 2 when the booster is given with a 2 or 3 month interval, while there is no decline in Ab titers post-dose 1. Whether Ab titers will continue to decline over time is not known. There are no long-term data when a boost is given 6 months post-dose 1.

CMI data are very limited (after 1 or 2 doses).

The potential impact of natural and of vaccine-induced anti-Ad26 immunity on immunogenicity remains unclear and should be further documented. This can have its importance if regular boosters are needed.

Homologous boosting with JCOVDEN induces lower antibody responses compared to heterologous boosting with a licensed mRNA vaccine after primary vaccination with JCOVDEN. Neutralising Ab titers reached at 1-month post-boost with JCOVDEN after primary vaccination with an mRNA vaccine are comparable to after a homologous boost with an mRNA vaccine.

Elderly and other subgroups:

Data are limited in the very old participants (aged 75 and older). No efficacy data were obtained in frail subjects and long-term health care residents.

Data are lacking in individuals with uncontrolled underlying disease and multiple comorbidities.

The subgroup analyses did not raise concern of lack of efficacy for particular subgroups for the two-dose schedule, but the number of cases (length of follow up) was very limited in some of the subgroups. Estimates were very imprecise in the elderly (60 years or more).

There are no data on immunocompromised persons due to condition or immunosuppressive therapy. Efficacy was lower in HIV+ participants, but numbers are small and data difficult to interpret without taking account of other characteristics and variants.

Asymptomatic infections:

Efficacy is lacking for asymptomatic cases, either after a single dose or after two doses of Ad26.COV2.S.

Asymptomatic COVID-19 cases were ascertained either based on serologic testing (seroconversion to the SARS-COV-2 N protein based on a Nucleoprotein assay) or a positive PCR. In practice most cases were identified bases on the Nucleoprotein assay. At the time of the final analysis of the double-blind phase of VAC31518COV3001, the estimated VE (adjusted 95% CI) against asymptomatic SARS-CoV-2 infection was 29% (20.0; 36.8) as of 28 days after vaccination. In the final analysis of VAC31518COV3009, efficacy against asymptomatic SARS-CoV-2 infection with onset at least 14 days after the second vaccination (96 cases reported) was 34% (-6.4; 59.8).

Viral load in respiratory samples:

Preliminary data suggest no relevant impact of vaccination with Ad26.COV2.S on SARS-CoV-2 viral load levels and duration of virus shedding in upper respiratory tract samples (nasal swabs) of COVID-19 cases in study VAC31518COV3001 and VAC31518COV3009.

Efficacy in seropositives:

In the final analysis of VAC31518COV3001, efficacy against moderate/severe COVID-19 was 76% (95% CI: 12.0; 95.7) in participants with serological evidence of past infection with SARS-CoV-2, based on only 12 events in the placebo arm and 3 in the active arm. The efficacy is not considered demonstrated in the individuals previously infected (lower bound of the CI not meeting the predefined success criterion). However, efficacy is anticipated in this group. The immunogenicity data, albeit limited, support this assumption.

Co-administration of other vaccines:

Concomitant administration with other vaccines has not been studied. A study evaluating the safety and immunogenicity of Ad26.COV2.S co-administrated with seasonal influenza vaccine is planned in the RMP, and currently ongoing.

Unfavourable effects

A single dose of Ad26.COV2.S has an acceptable safety and reactogenicity profile in adults 18 years of age or older, including adults older than 60 years of age. The safety profile of the primary vaccination with Ad26.COV2.S in adults described in the current SmPC is based on a primary pooled analysis of clinical safety data from the double-blind phase of Phase 3 studies (VAC31518COV3001 and VAC31518COV3009) and of Phase 1 and Phase 2 clinical studies (COV1001, COV1002, COV2001) with Ad26.COV2.S 5×10^{10} vp (18 November 2021) (procedure EMEA/H/C/005737/II/0060 approved after the renewal reporting interval) and on post-marketing data which became available following the initial authorization of the vaccine.

The safety of Ad26.COV2.S is mainly characterised by local and systemic reactions. Reactions were mostly mild to moderate, transient and generally resolved within 1 to 2 days post-vaccination. The reactogenicity was milder and lower in older adults. The overall frequency of SAEs (not associated with COVID-19) was low and balanced between placebo and active groups. The safety profile was generally consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline.

The administration of Ad26.COV2.S as an homologous booster dose after a primary vaccination with Ad26.COV2.S or as an heterologous booster dose (following completion of primary vaccination regimen with a mRNA COVID-19 vaccine or an adenoviral vector-based COVID-19 vaccine) has also an acceptable safety and reactogenicity profile in individuals 18 years of age and older, with no new safety concerns identified (procedure EMEA/H/C/005737/II/0053/G approved after the renewal reporting interval).

From launch up to 31 July 2022, it is estimated that over 52 million doses of Ad26.COV2.S were administered worldwide. Increasing experience based on spontaneous/solicited post-marketing reporting of adverse events, have led to the identification of new, some serious (sometimes fatal), adverse events/reactions (including new recognized ADRs in currently published SmPC: thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome (GBS), Capillary leak syndrome, lymphadenopathy, paraesthesia and hypoesthesia, dizziness, diarrhoea, vomiting, and tinnitus, VTE, and immune thrombocytopenia; and transverse myelitis) for which causality with the Ad26.COV2.S vaccine has been concluded, based on the available data. TTS, GBS, thrombocytopenia, including immune thrombocytopenia, and venous thromboembolism are important identified risks. TTS is in particular of concern (with some fatal outcomes) and, as specified in the SmPC, TTS cases occurred within the first three weeks following vaccination, and mostly in individuals under 60 years of age. Overall, these risks occur very rarely, are adequately monitored and relevant risk minimisation measures have been proposed. Potential safety concerns will continue to be monitored.

The most recent clinical AdVac safety database report (V7.0, dated 1 July 2022) has been assessed in the PAM EMEA/H/C/005737/REC/019.1 (approved after the renewal reporting interval). A total of 48,744 participants have been vaccinated with an Ad26-based vaccine in 42 clinical studies that have been integrated in the AdVac Safety Database V7 (cut-off date of 31 December 2021). They were mainly adults (47,944 adults) and from COVID-19 vaccine studies (39,623 adults: 21,898 in VAC31518COV3001 and 15,707 in VAC31518COV3009). Overall, Ad26-based vaccines were safe and well tolerated based on the data currently available in the clinical database.

Uncertainties and limitations about unfavourable effects

The uncertainties and limitations of unfavourable effects have been discussed in other procedures. The principal uncertainties are related to long-term effects, interactions with other vaccines and effects in specific risk groups.

As described in the RMP, Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), remains an important potential risk. It is noted that the current dataset gives no indication of vaccine-enhanced disease.

Finally, the current post authorisation exposure is insufficient to establish differences in the onset and severity of the very rare ADRs between primary and booster usage of Ad26.COV2.S.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Efficacy of a single dose of JCOVDEN was assessed in a multi-country trial during a period with a high diversity of variants. Efficacy against moderate/severe COVID-19 was 56% (95% CI: 51.3; 60.8) over a 4-month median follow-up period. Efficacy against severe COVID-19 was 73% (95% CI: 63.9; 80.5).

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for elderly (≥65 years), as well as for participants with medical comorbidities associated with high risk of severe COVID-19.

A drop of efficacy against moderate/severe was observed rapidly after a single dose (a few weeks following vaccination), in parallel with the progressive disappearance of the reference strain and emergence of several variants. In contrast, efficacy against severe COVID-19 was maintained at least

up to 6 months following a single dose of Ad26.COV2.S. Persistence of efficacy beyond 6 months after a single dose is not known, as efficacy data are not available after this timepoint.

Efficacy of a two-dose schedule of JCOVDEN, administered two months apart, was estimated in a multi-country trial while Alpha and Mu were the two dominant variants. Efficacy against moderate/severe COVID-19 was 75% (95% CI: 54.6; 87.3) over a median FU period of 36 days. There were too few severe cases to estimate the efficacy.

During both efficacy studies, there was limited circulation of the Delta variant, and the Omicron variant was not yet circulating. The limited data suggest a lack of efficacy for the Delta variant. There is no efficacy data for Omicron.

Efficacy of JCOVDEN used as homologous or heterologous booster is not known (refer to EMEA/H/C/005737/II/33).

There are limited real-world data for the use of JCOVDEN as primary vaccination or homologous/heterologous boost in the context of the Delta wave. Overall, one dose of JCOVDEN induces overall good protection against severe disease, similar to other/previously circulating variants.

One dose of JCOVDEN elicits both humoral and cellular immune responses as early as 14 days, in both young and older adults.

Both an homologous and heterologous boost given at least 2 or 3 months after the primary vaccination with JCOVDEN and mRNA vaccine, respectively, induces an increase in both neutralizing and binding Ab against the original strain and the Delta variant (binding Ab), when compared to pre-boost values. A heterologous boost with JCOVDEN after primary vaccination with an adenoviral vector-based vaccine is also immunogenic (approved outside the period covered by this annual renewal).

The clinical relevance of these findings is not known as there is no established immunological correlate of protection.

The potential impact of natural and of vaccine-induced anti-Ad26 immunity on immunogenicity remains unclear and should be further documented. This can have its importance if regular boosters are needed.

A single dose of Ad26.COV2.S, and the administration of Ad26.COV2.S as an homologous booster dose after a primary vaccination with Ad26.COV2.S or as an heterologous booster dose (after completion of a 2-dose primary vaccination regimen with a mRNA COVID-19 vaccine or with an adenoviral vector-based COVID-19 vaccine), have an acceptable safety and reactogenicity profile in adults ≥18 years of age.

The safety of Ad26.COV2.S is mainly characterised by local and systemic reactions. Reactions were mostly mild to moderate and transient. The reactogenicity was milder and lower in older adults. The overall frequency of SAEs (not associated with COVID-19) was low and balanced between placebo and active groups. The safety profile was generally consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline.

From launch up to 31 July 2022, it is estimated that over 52 million doses of Ad26.COV2.S were administered worldwide. Increasing experience based on spontaneous/solicited post-marketing reporting of adverse events, have led to the identification of new, some serious (sometimes fatal), adverse events/reactions. TTS, GBS, thrombocytopenia, including immune thrombocytopenia, and venous thromboembolism are important identified risks. TTS is in particular of concern (with some fatal outcomes) and, as specified in the SmPC, TTS cases occurred within the first three weeks following vaccination, and mostly in individuals under 60 years of age. Overall, these risks occur very rarely, are

adequately monitored and appropriate risk minimisation measures have been proposed. Potential safety concerns will continue to be monitored as detailed in the RMP.

Balance of benefits and risks

Based on the cumulative evidence in terms of favourable and unfavourable effects, the benefit-risk balance of JCOVDEN remains positive.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

Several quality-related SOBs have been raised with regards to remaining validation and comparability data for the implementation of additional manufacturing sites for both the active substance and the finished product. All remaining data have been provided and were found acceptable. Therefore, it can be concluded that these quality-related SOBs have been adequately addressed and can be considered resolved.

Considering the vaccination of a large proportion of the control arm and the possibility for all participants to be administered with a booster vaccine (Ad26.COV2.S or other approved COVID-19 vaccine), it is considered that the continued follow-up would no longer contribute in a significant way to the safety and efficacy profile substantiate the safety and efficacy profile of JCOVDEN. It is not expected that the remaining outstanding data from study VAC31518COV3001 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of the vaccine.

Based on the comprehensive data available from multiple sources, it is agreed that the remaining specific obligations regarding VAC31518COV3001 may be reclassified as Category 3 study in the RMP, with the final CSRs to be submitted at a later stage as supportive data. There are no remaining grounds for the marketing authorisation to remain conditional and the CHMP therefore recommends the granting of a standard marketing authorisation not subject to Specific Obligations for of JCOVDEN.

7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for JCOVDEN in its approved indication(s) (please refer to the Summary of Product Characteristics) continues to be favourable. As all specific obligations have either been fulfilled or reclassified as category 3 study in the RMP, there are no remaining grounds for the marketing authorisations to remain conditional and the CHMP therefore recommends the granting of a standard marketing authorisation not subject to Specific Obligations for JCOVDEN.

Amendments to the marketing authorisation

In view of the data submitted with the annual renewal, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a full marketing authorisation not subject to Specific Obligations. As a result, it is recommended that the final study report for the ongoing clinical trials are reclassified as category 3 study in the RMP and are therefore deleted from the Annex II to this opinion.

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.