EMA/757560/2021
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/0023

Invented name: COVID-19 Vaccine Janssen

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

Marketing authorisation holder (MAH): Janssen-Cilag International N.V.

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:	18 Oct 2021	18 Oct 2021
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	16 Nov 2021	16 Nov 2021
☐	CHMP and PRAC members comments	22 Nov 2021	22 Nov 2021
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	25 Nov 2021	N/A
☐	PRAC endorsed relevant sections of the assessment report	02 Dec 2021	02 Dec 2021
☒	Opinion	16 Dec 2021	16 Dec 2021

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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 COVID-19 Vaccine Janssen (also referred to as Ad26.COV2.S). 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 10 September 2021 an application for renewal of the conditional MA for COVID-19 Vaccine Janssen. The expiry date of the MA is 11 March 2022.

The period covered by this annual renewal is 25 February 2021 to 31 July 2021.

2. Specific Obligations

Table 1. Specific Obligations as adopted by the CHMP

Reference	Description	Status
SOB related to AS	In order to confirm the consistency of the active substance (AS) manufacturing process, the MAH should provide additional comparability and validation data.	Partially fulfilled
SOB related to FP	In order to confirm the consistency of the finished product (FP) manufacturing process, the applicant should provide additional validation and comparability data.	Partially fulfilled
SOB related to clinical	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.	Not fulfilled

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

Quality-related SOBs

- **SOB related to the AS: In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data.**

A SOB related to the active substance was added following Variation IB/11 to upgrade the AS facility at Janssen Biologics Leiden (Netherlands). Please refer to Table 2 for a detailed overview of the quality SOBs. Interim reports related to this SOB have been submitted and evaluated, the final report has been submitted and the assessment of type II/37 is ongoing.

It should be noted that the same SOB may apply to future variations to implement additional manufacturing sites, this overarching SOB (applicable to various manufacturing sites) cannot be considered closed for the time being and should therefore remain in the Annex II.

At time of approval of the conditional marketing authorisation in March 2021, the following quality-related specific obligation was included in Annex II.

- **SOB related to the FP: In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.**

At the time of approval of the conditional marketing authorisation in March 2021, this SOB only referred to the Catalent Bloomington, Indiana (USA) Finished Product manufacturing site. In the meantime, the MAH has provided the remaining validation and comparability data for the Catalent Bloomington, Indiana (USA) site as requested in this SOB. The data have been assessed and were found acceptable. Accordingly, the specific obligation related to the Catalent Bloomington Indiana (USA) site can be considered as fulfilled.

However, this SOB was afterwards also applied to several variations which have been submitted post-approval of the conditional MA to implement additional FP manufacturing sites in the conditional MA: Aspen (South-Africa), IDT Biologika (Germany), Catalent Anagni (Italy), Merck Sharp & Dohme West Point (USA) and Sanofi Pasteur Marcy l'Etoile (France), These FP manufacturing sites were also conditionally approved via variation procedures with the specific obligation to provide additional validation and comparability data.

For the Aspen (South Africa) site, the remaining validation and comparability data have also been provided. The data have been assessed and were found acceptable. Accordingly, the specific obligation related to the Aspen site (South Africa) can also be considered as fulfilled.

For the IDT Biologika (Germany) site, the remaining validation and comparability data have also been provided. The data have been assessed and were found acceptable. Accordingly, the specific obligation related to the IDT Biologika (Germany) site can also be considered as fulfilled.

For the other FP manufacturing sites (Catalent Anagni Italy, Merck Sharp & Dohme West Point USA and Sanofi Pasteur Marcy l'Etoile France), the assessment of the data as requested by the SOB related to the FP is still ongoing or the submission of the data is pending in accordance with the agreed timelines. For some of these sites, interim reports have been provided with partial and/or preliminary data which were all found acceptable thus far. Please refer to Table 2 for a full overview of the quality SOBs.

All interim reports and final reports related to as and FP SOBs for the various manufacturing sites have been submitted before the specific due date for each data package (as approved in the conditional MA and the respective Variation reports).

Taken together, whereas these SOBs relates to different FP and AS 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 SOBs ("*In order to confirm the consistency of the finished product manufacturing process, 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/indicating the validates status of the process. For the Catalent Bloomington, Indiana (USA) site, the Aspen (South Africa) and the IDT Biologika (Germany) sites, this SOB can be considered as fulfilled. For the other sites, assessment is still ongoing or pending the submission of the interim report and final reports in line with the agreed due dates.

It should be noted that these SOBs may be applied to future variations as well (for additional FP and AS manufacturing sites).

As such, since assessment of FP and AS SOBs is still ongoing for several manufacturing sites and since

these SOBs may also be applied to future variations to implement additional manufacturing sites, these overarching SOBs (applicable to various FP and AS manufacturing sites) cannot be considered closed for the time being. For a detailed overview of the Quality SOBs, please refer to Table 2.

Table 2: Overview of quality SOBs

SOB related to the AS	In order to confirm the consistency of the active substance manufacturing process, the MAH should provide additional comparability and validation data. This SOB was added with procedure IB/11 (to introduce process changes and a modification of the Janssen Biologics B.V. Drug Substance (DS) manufacturing site in Leiden, the Netherlands). • First Interim report: 03 August 2021- fulfilled • Second Interim report: 13 August 2021 - fulfilled • Final report: 30 November 2021 – submitted - Type II/37 is currently under evaluation with opinion date 10 February 2022	30 November 2021
SOB related to the FP	In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data. This SOB includes several finished product manufacturing sites: 1) Catalent Bloomington, Indiana (USA) site added during the CMA procedure: - Interim report: 31 March 2021 – fulfilled - Final report: 15 August 2021- fulfilled 2) Aspen (South Africa) site added with procedure IB/001/G: - First report: 19 April 2021- fulfilled	30 June 2022

	- Second report: 31 May 2021- fulfilled - Final report: 30 September 2021- fulfilled with type II/26/G (opinion on 16 Dec 2021) 3) IDT Biologika (Germany) site added with procedure IB/002/G: - First report: 27 April 2021- fulfilled - Final report: 31 May 2021- fulfilled with Type II/05 (opinion on 24 May 2021) 4) Catalent Anagni (Italy) site added with procedure IB/008: - First report: 16 July 2021 - fulfilled - Second report: 30 Sept 2021- fulfilled - Third report: 31 Dec 2021- not yet fulfilled - Final report: 31 March 2022- not yet fulfilled 5) Merck Sharp & Dohme Corp, West Point (USA) site added with procedure IB/025/G: - First report: 20 Dec 2021- not yet fulfilled - Final report: 31 May 2022- not yet fulfilled 6) Sanofi Pasteur Marcy L'Etoile (France) site added with procedure IB/036: - First report: 31 Jan 2022- not yet fulfilled - Second report: 31 Jan 2022- not yet fulfilled - Final report: 31 June 2022- not yet fulfilled	

Clinical-related SOBs

The status of the clinical Specific Obligations are provided below:

Description	Procedural number	Status
Clinical Specific Obligations: 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.		
From initial conditional MA: The MAH should submit the final Clinical Study Report (CSR) for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	N/A	As informed during the meeting held on 17 June 2021, final analysis (end of double-blind phase) on COV3001 will not be available for submission in the renewal. Given that a submission of data on COV3001 is expected in Q42021, as agreed during the meeting held on 17 June, the annual renewal will therefore focus on information related to accrual, conduct of the study and MAH conclusion on feasibility of concluding study on time only.
From initial conditional MA: Submission of final CSR for VAC31518COV3001 by 31 December 2023	N/A	Final CSR (including long-term follow-up) is on track for submission by 31 December 2023. The CSR for the final analysis of the double-blind phase is planned in the last quarter of 2021.

2.1. Outstanding Specific Obligations – status report for period covered

SOB (quality-related)

In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data.

A SOB related to the active substance was added following Variation IB/11 to upgrade the AS facility at Janssen Biologics Leiden (Netherlands). Please refer to Table 2 for a detailed overview of the quality SOBs. Interim reports related to this SOB have been submitted and evaluated, the final report has been submitted and the assessment of type II/37 is ongoing.

It should be noted that the same SOB may apply to future variations to implement additional manufacturing sites, this overarching SOB (applicable to various manufacturing sites) cannot be considered closed for the time being and should therefore remain in the Annex II.

In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.

A SOB initially related to the Catalent Bloomington (US) site in the conditional MA. For this site, the requirements as stated in the SOB have been fulfilled. However, the same SOB has afterwards also been applied to other manufacturing sites implemented post-approval of the conditional MA via Variation procedures. Since assessment of SOB is still ongoing for several manufacturing sites and

since this SOB may also be applied to future variations to implement additional manufacturing sites, this overarching SOB (applicable to various manufacturing sites) cannot be considered closed for the time being.

In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.

The Rapporteur is of the opinion that Specific Obligation SOB has been fulfilled, i.e. for the Catalent Bloomington (USA) site, Aspen (South Africa) and the IDT Biologika site (Germany).

However, the same SOB also applies to several other manufacturing sites which were implemented post-approval of the conditional MA via Variations. Since assessment of SOB is still ongoing for several manufacturing sites and since this SOB may also be applied to future variations to implement additional manufacturing sites, this overarching SOB (applicable to various manufacturing sites) cannot be considered closed for the time being and should therefore remain in the Annex II.

SOB (clinical-related)

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.

The CSR for the final analysis of the double-blind phase of the pivotal Phase 3 COV3001 study is not yet available. Given that a date for submission of data for the final analysis of the double-blind phase of COV3001 is expected in the fourth quarter of 2021 (Q4 2021), it was agreed with EMA in a meeting held on 17 June 2021 that the annual renewal would focus on information related to accrual, conduct of the study and a conclusion provided by the MAH with respect to the feasibility of concluding the study on time. This information is described below.

As of the cut-off date for the final analysis of the double-blind phase (09 July 2021), 49,497 participants have been screened, of whom 43,788 were randomized to receive the study vaccine in a 1:1 ratio (Ad26.COV2.S [5×10^{10} vp]/placebo). As of the 09 July cut-off, 95.5% of participants were ongoing and 4.5% discontinued prematurely.

As of protocol Amendment 3, study participants who became eligible to receive an authorized/licensed COVID-19 vaccine during the course of the study could request to be unblinded for this purpose. As of protocol Amendment 4, after Emergency Use Authorisation (EUA) in the United States (US) and conditional MA in the EU, unblinding of all participants was initiated and participants in the placebo group were offered a single dose of Ad26.COV2.S. Unblinded participants, whether in the vaccine or control group, were encouraged to continue to be followed in this study. A total of 13,703 participants from the placebo group have been vaccinated in the open-label phase (crossover).

The final analysis of the double-blind phase of COV3001 is ongoing. The CSR for the final analysis of the double-blind phase will be available in the fourth quarter of 2021. The specific obligation for COV3001 linked to the conditional MA is as follows: "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," and needs to be fulfilled by 31 December 2023. Based on the current status of COV3001, the MAH confirms the date of 31 December 2023 for completion of this specific obligation is feasible.

In conclusion, the Clinical SOB has not been fulfilled during this annual renewal. The MAH plans to complete this SOB by December 2023.

2.2. Overall conclusion on Specific Obligations

In relation to the quality related SOBs, new data regarding FP and AS SOBs has emerged during the period covered by this annual renewal. The new data emerged are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted. The Specific Obligation related to the FP has been fulfilled for the Catalent Bloomington (USA), Aspen (South Africa) and the IDT Biologika (Germany) sites. However, the same SOB also applies to several other manufacturing sites which were implemented post-approval of the conditional MA via variations. Since the assessment of FP and AS related SOBs is still ongoing for several manufacturing sites and since these SOBs may also be applied to future variations to implement additional manufacturing sites, these overarching SOBs (applicable to various manufacturing sites) cannot be considered closed for the time being and should therefore remain in the Annex II.

In relation to the clinical SOB, no new data has emerged during the period covered by this annual renewal. Based on the current status of COV3001, the MAH confirms the date of 31 December 2023 for completion of this specific obligation is feasible ("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."). The SOB is still not fulfilled, the final clinical study report is due on 31 December 2023.

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

3.1. Quality

Apart from the SOBs, the applicant has also provided additional quality data related to the recommendations.

At time of approval of the conditional MA, a list of 14 recommendations (REC)/ post-authorisation measures, (PAM) was included.

PAMs 1, 2, 3, 5, 6, 7, 8, 9, 10 and 13 have been fulfilled.

REC 1: The applicant has provided the validation data of the third process validation inoculum batch.

REC 2: The MAH has provided the results of the tier 2 comparability testing for the DS lots manufactured by the 900L scale process at Janssen Biologics Leiden. All results were comparable with those of DS lots/intermediates from the other registered sites and/or process scales for all parameters. These data confirm that DS lots manufactured at Janssen Biologics Leiden using the large scale 900L process are comparable with DS material form the registered sites and/or process scales.

REC 3: The MAH has provided the results of the tier 2 comparability testing for the DS lots manufactured by the 900L scale process at Emergent (US). All results were comparable with those of DS lots/intermediates from the other registered sites and/or process scales for all parameters. These data confirm that DS lots manufactured at Emergent (US) using the large scale 900L process are comparable with DS material form the registered sites and/or process scales.

REC 5: The MAH has provided CTD sections describing the vial depyrogenation and the decontamination of the filling line at the Catalent Indiana site.

REC 6: The MAH has provided the tier 2 comparability data for the GRAM (US) site. All results were comparable with those of the phase 3 clinical DP lots. These data confirm that DP manufactured at the GRAM site (US) is comparable to the phase 3 clinical DP lots.

REC 7: The MAH has provided validation data for the GRAM DP manufacturing site confirming homogeneity of the final bulk after mixing and of the final vaccine after filling. The results show that the DP process ensures homogeneity of the final bulk and the filled vaccines. Also hold times were confirmed.

REC 8: To 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 by 30 September 2021.

REC 9: The MAH has provided the results from the forced degradation studies using thermal stress conditions at 37ºC for up to 28 days, which were part of the comparability analysis between clinical Phase 1/2 lots and phase 3 lots. The data confirm the comparability.

REC 10: A final conclusion has been provided on the criticality of the potentially critical process parameters.

REC 13: The MAH as performed an elemental impurity risk assessment in accordance with ICH Q3D. The assessment showed that the risk for elemental impurities in Covid-19 Vaccine Janssen drug product is negligible.

Five PAMs (recommendations 4, 11, 12 and 14) are still open and are detailed below. The data should be provided as soon as possible when available.

- The applicant is requested to initiate stability studies (including at least 3 representative lots) for the 900L scale AS process at Janssen Biologics (Leiden, NL). The applicant is requested to provide the AS stability data for 3 representative AS batches for each manufacturing scale (50L and 900L) when the respective studies have been finalised and the results are available.
- The applicant is requested to provide the results of the 6-month time point of the FP container leachables study.
- Regarding the FP specification for polydispersity, the applicant is requested to establish and justify acceptance criteria once sufficient experience and data for this parameter are available.
- The applicant is requested to provide the FP stability data for the 3 FP PPQ batches from the GRAM site when the stability studies have been finalised and the results are available.

3.2. Non-clinical

No non-clinical studies initiated or completed during the reporting period were submitted, nor any other new additional nonclinical information to report.

3.3. Clinical efficacy and immunogenicity

No new efficacy or immunogenicity data have been submitted since the initial MAA.

Recommendations (as stated at initial conditional MA):

Description	Recommended within Proc. No
The MAH is requested to provide the validation report of the SARS-CoV-2 microneutralization assay (WT-MNA), which would include an external validation with international reference standard material (as soon as possible).	EMEA/H/C/005737
The MAH is requested to test the in-house developed S protein-ELISA with international reference standards and provide the result (as soon as possible).	EMEA/H/C/005737
With results submission obtained with the N protein-ELISA, the MAH is requested to give clarification on how the data were interpreted (as soon as possible).	EMEA/H/C/005737
The MAH is requested to provide validation reports IFN-γ and IL-4 ELISpot assays with final CSR (as soon as possible).	EMEA/H/C/005737
Regarding the CD4 and CD8 Th1 immune responses induced following vaccination in study VAC31518COV1001 and VAC31518COV2001, the MAH is requested to provide median of responses based on positive samples only and comparison between group in the final CSR (as soon as possible).	EMEA/H/C/005737
The MAH is requested to discuss if the qualification (and validation) results of the initial WT-MNA could be generalised to MNA based assay using different strains and/or whether this will be addressed (as soon as possible).	EMEA/H/C/005737
The MAH is requested to provide data on cross-neutralization for clinically relevant and emerging SARS-CoV-2 strains by testing sera of human clinical participants (particularly of study VAC31518COV3001 in functional in vitro assays) (as soon as possible).	EMEA/H/C/005737

The applicant is requested to present the plan regarding the assessment of the vaccine performance against emerging variants and/or performance of a new vaccine construct (including the Spike protein from a variant of concern) in protecting against COVID-19 if it appears that a new construct vaccine is needed in the future (as soon as possible).	EMEA/H/C/005737
The MAH should justify why, in study VAC31518COV2001, the anamnestic response will be assessed after a shorter interval between the primary vaccination and the antigen presentation for the 2-dose schedule when compared to the 1-dose schedule (final CSR) (as soon as possible).	EMEA/H/C/005737
The MAH is requested to present the data on (and discuss) the impact of the natural and vaccine-induced immunity to the Ad26 vector on the insert-specific vaccine-induced immune responses by COVID-19 study, overall for the COVID-19 program and overall for Ad26-based vaccination. In addition, the population of COV3001 should be described according to baseline immunity to the vector. The Applicant should provide this data in the final CSR (as soon as possible).	EMEA/H/C/005737
For study COV3001, the MAH should provide the baseline comorbidities leading to higher risk of severe disease of the subjects included in the immunogenicity subset and of those included in the subset used for the additional binding Ab analysis (or any other analysis) (as soon as possible).	EMEA/H/C/005737
For study COV3001, the MAH should present the plan on the immune correlate of protection and provide results when available (as soon as possible).	EMEA/H/C/005737
For study COV3001, the MAH should provide plans to address waning of immune responses and vaccine efficacy, and the need for and timing of booster, in the context of crossover vaccination and resulting loss of placebo-controlled follow up. Provide SAP including these plans (including analyses at 6 months FU and before cross-over). The Applicant is recommended to seek further interaction via EMA Scientific Advice on these points (as soon as possible).	EMEA/H/C/005737
For study COV3001, the MAH should provide cross-tabulation data linking seroconversion and RT-PCR results, for the various case definitions (symptomatic, mild, moderate to severe/critical COVID-19) (as soon as possible).	EMEA/H/C/005737
For study COV3001, the MAH should provide validation document of whole genome sequencing assay (as soon as possible).	EMEA/H/C/005737
For study COV3001, the MAH is planning an immunogenicity trial in immunocompromised (IC) participants. Considering the lack of an ICP, and the heterogeneous nature of IC populations, the MAH is recommended to seek EMA Scientific Advice on the study design (as soon as possible).	EMEA/H/C/005737
For study COV3001, there are differences in terms of follow up duration affect the comparisons of efficacy across age groups and across participants with/without comorbidities. Differences in terms of timing of vaccination could also affect the interpretation of certain subgroup analyses (given the emergence of variants for which efficacy could vary). The MAH needs to provide analyses (such as stratified/adjusted) taking account of these factors for an appropriate interpretation of the subgroup analyses. A discussion is expected, including an analysis of the biases that could have affected the subgroup analyses (as soon as possible).	EMEA/H/C/005737
For study COV3001, a detailed description of the cases found in seropositive participants, including genomic analysis, is expected in the final report to ensure an accurate assessment of the cases. Without details, whether these cases were real re-infection or rather re-detection cannot be assessed. Any relevant information should be included in	EMEA/H/C/005737

a table for each case, such as time of onset, age, country, genome sequencing etc (as soon as possible).	
For study COV3001, when submitting updated data on asymptomatic cases as part of a further report, the MAH should present these data by variant, and include a discussion on the sources of biases (such as biases related to varying efficacy and clinical expression of disease across variants, differences in terms of follow up duration for the assessments of the endpoint) (as soon as possible).	EMEA/H/C/005737
For study COV3001, in addition to the planned endpoint 'asymptomatic or undetected COVID-19' based on PCR and seroconversion to the N protein, the analysis used an endpoint based on 'seroconversion only'. An endpoint considering all seroconversions to the N protein (irrespective of the PCR result) appears more relevant and should be presented as well (as soon as possible).	EMEA/H/C/005737
For study COV3001, in the final CSR, the MAH should present the concordance between PCR results and seroconversion for the N protein serology, in symptomatic and asymptomatic cases with PCR results available (from the central lab, and from any source) (as soon as possible).	EMEA/H/C/005737
In study COV3001, to assess the impact of excluding subjects with missing SARS-CoV-2 serology status at baseline, a sensitivity analysis of VE on subjects seronegative at baseline only should be performed (as soon as possible).	EMEA/H/C/005737
The MAH should submit the 6 month and 1 year interim Clinical Study Reports for the randomised, placebo-controlled, observer-blind study VAC31518COV3001 (as soon as possible).	EMEA/H/C/005737
The MAH should submit the 6 month and 1 year interim and final Clinical Study Reports for the randomised, placebo-controlled, observer-blind study VAC31518COV3009 (as soon as possible).	EMEA/H/C/005737
The MAH should evaluate the feasibility of including "Exacerbation of chronic pulmonary disorders (ie, asthma)" as an endpoint in study VAC31518COV4003, and the results should be provided as available (a soon as available).	EMEA/H/C/005737

3.4. Clinical safety

The initial safety profile of Ad26.COV2.S was established based on the COV3001 data available at the time of the conditional MA. Since then, Ad26.COV2.S was administered in further clinical trials and more than 25 million doses of Ad26.COV2.S have been administered worldwide. The safety profile of the Ad26.COV2.S is monitored through routine safety pharmacovigilance activities (such as signal detection, Monthly Summary Safety Reports (MSSRs)) for which the results were reflected in the EU-RMP updates and updates to the SmPC during the reporting period.

Exposure

Exposure clinical trials

Table 3 Clinical trial exposure data for Ad26.COV2.S

Clinical Trials Ad26.COV2.S	Blinding status	Ad26. COV2.S	Placebo	Blinded	Total	Crossover
COV1001	Unblinded	881	195	-	1076	52
COV1002	Unblinded	200	50	-	250	-
COV1003	Unblinded	380	-	-	380	-
COV2001	Blinded	-	-	617[b]	617	-
COV3001	Unblinded	21,895	21,888	-	43,783	13,735
COV3003	Blinded	-	-	253	253	-
COV3009	Blinded	-	-	31,706	31,706	-
Total estimated clinical exposure#		23,356	22,133	32,576	78,065	13,787
Person-years follow-up[a]		10,271.42	10,664.69	10,031.98	-	-

* Note: Clinical studies COV2001, COV3003 and COV3009 are blinded so the number of participants receiving Ad26.COV2.S is an estimate based on randomization ratio.
# Total estimated exposure from the clinical trial databases for Ad26.COV2.S.
[a] From randomization until latest attended visit.
[b] 33 adolescents have been recruited in this trial.
Data Lock Point (cut-off date) for COV1001 of 04AUG2021, COV1002 of 04AUG2021, COV1003 of 02AUG2021, COV2001 of 03AUG2021, COV3001 of 27JUL2021, COV3003 of 02AUG2021, and COV3009 of 05AUG2021.

Post-marketing exposure

A total of 57,783,400 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 31 July 2021.

An estimated 25,703,249 individuals were administered the Ad26.COV2.S vaccine worldwide from launch to 31 July 2021.

As of 31 July 2021, cumulative post-marketing exposure in the United States is a total of 13,408,923 administered doses of Ad26.COV2.S according to the Center of Disease Control (CDC 2021). As of 31 July 2021, cumulative post-marketing exposure in the European Union/EEA is a total of 11,164,557 administered doses of Ad26.COV2.S according to the European Centre for Disease Prevention and Control (ECDC 2021).

Table 4 Cumulative Patient exposure to Ad26.COV2.S vaccine through to 31 July 2021

Region/Country	Number of Distributed Doses[a]	Number of Patients Exposed/ Number of Administered Doses[b]
EEA		
Austria	320,400	192,084
Belgium	629,200	311,927
Bulgaria	123,700	75,703
Croatia	112,750	45,245
Cyprus	29,700	17,561
Czechia	247,200	129,449
Denmark	694,800	47,605
Estonia	46,000	35,153
Finland	68,400	-
France	2,379,800	712,051
Germany	4,660,650	2,332,229
Greece	600,000	327,778
Hungary	550,800	116,499
Iceland[c]	21,500	52,952
Ireland	281,500	212,076
Italy	2,370,000	1,336,031
Latvia	110,200	91,870
Lithuania	92,800	76,766
Luxembourg	41,800	32,227
Malta	34,800	10,681
Netherlands	1,432,800	760,862
Norway	283,200	2,157
Poland	2,160,100	1,333,699
Portugal[c]	578,400	616,823
Romania	1,081,300	412,663
Slovakia	180,000	30,030
Slovenia	120,000	65,134
Spain	2,659,000	1,787,302
Sweden	310,300	0
ROW		
Brazil	1,801,550	-
Colombia	480,000	-
South Africa	3,008,000	-
South Korea[c,d]	100,800	1,129,769
US	**30,171,950**	**13,408,923**
Total	**57,783,400**	**25,703,249**

Key: CDC=Centers for Disease Control and Prevention, ECDC=European Centre for Disease Prevention and Control, EEA=European Economic Area; KDCA=Korea Disease Control and Prevention Agency; ROW=Rest of World; US=United States.

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

b: Number of vaccine doses administered were reported from CDC for the US, from ECDC for EEA countries, and from KDCA for South Korea.

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

d: Vaccine administration data is available from 10 June 2021 onwards.

Exposure Study COV3012

The non-Company-sponsored COV3012 (Sisonke) study, hereby referred to as COV3012, is an open-label, single-arm, Phase 3b implementation study to monitor the safety of the single-dose Ad26.COV2.S vaccine (5x1010 vp) among health care workers in South Africa. As it is a single-arm study, no effectiveness objectives have been prespecified in the Sisonke study. No electronic case report forms (eCRFs) are available for this trial. However, serious adverse events (SAEs) are captured and reported in the Global Medical Safety (GMS) database. As of 31 July 2021, a total of 490,863 participants in the Sisonke study received a single dose of the Ad26.COV2.S vaccine.

Overview of signals

Data related to the below signals were carefully reviewed through MSSRs or relevant signal procedures leading to several requests to update the product information and EU-RMP.

Signals Confirmed as Important Identified Risks

Thrombosis with Thrombocytopenia Syndrome (TTS)

A signal evaluation (EPITT number: 19689) was performed investigating TTS in relation to the compound. As a result, the RMP and SmPC section 4.8 was updated to include TTS as identified risk in the RMP and as adverse drug reaction (ADR) in the SmPC section 4.8 (EMEA/H/C/005737/IA/0004, EMEA/H/C/005737/IA/0003 and EMEA/H/C/005737/II/0006/G).

Guillain-Barré syndrome (GBS)

Based on the observation of a disproportionality of spontaneous/solicited post-marketing reports of cases of GBS in the MSSR and an assessment of possible causality with the Covid-19 vaccine Janssen, the SmPC sections 4.4 and 4.8 were updated with GBS in the frame of procedure EMEA/H/C/005737/II/0012. Additionally, the RMP was updated to include GBS as an Important Identified Risk in the list of safety concerns.

Signals Confirmed as Important Potential Risks

Thromboembolic events are currently being assessed by the MAH in the MSSR, and additional safety data will be submitted in line with the PRAC request of the PRAC Assessment Report for the 5th pandemic safety update MEA 014.4 dated September 2, 2021.

Thrombocytopenia

In line with recommendations from EMA PRAC received on 05 August 2021 in response to the MSSR (EMEA/H/C/005737/MEA/014.3), the MAH has submitted a Type II variation on August 25, 2021 (EMEA/H/C/005737/II/0020) to update the SmPC, to include immune thrombocytopenia (ITP) as an ADR with a frequency "not known" (Section 4.8 of the SmPC). A warning and precaution statement relating to observation of very low platelet levels following vaccination with Ad26.COV2.S will be included in Section 4.4 of the SmPC. ITP was furthermore included as important identified risk in the RMP.

Initially, the MAH proposed to update the RMP version 2.2 to include `thrombocytopenia´ as an important potential risk. However, due to additional information regarding ITP that led to the inclusion of this event in section 4.8 of the SmPC of the product information (EMEA/H/C/005737/II/020), the MAH proposed to add 'Immune Thrombocytopenia' instead of 'Thrombocytopenia' and re-classify the safety concern to important identified risk. The addition of ITP as an important identified risk was endorsed. It was nevertheless not agreed to narrow the term 'thrombocytopenia' to ITP since 'thrombocytopenia' remains an important safety concern which has not been sufficiently characterized at this stage to allow a narrowing of the definition

Furthermore, the case definition of ITP proposed by the MAH (2018 ITP definition by the American Society of Hematology (Kelton 2018) has been questioned in another procedure

(EMEA/H/C/005737/II/018) that was finalized after the cut-off for this renewal procedure. The RMP was to be updated with the definition of ITP in line with the outcome of EMEA/H/C/005737/II/018.

Signals Confirmed as Identified Risks Not Categorized as Important (New Adverse Drug Reactions)

Late Breaking information on additional ADRs that were identified by the MAH for inclusion in the SmPC is provided below.

As part of the regular safety monitoring activities, the following events were identified as validated post-marketing safety signals: lymphadenopathy, paraesthesia, hypoesthesia, diarrhoea, vomiting, and tinnitus. These events were mostly reported as nonserious.

Capillary Leak Syndrome (CLS)

The SmPC section 4.3 has been updated to include a contraindication for individuals who have previously experienced episodes of CLS (EMEA/H/C/005737/II/0010). The MAH should continue to monitor CLS and present results in upcoming MSSRs and Periodic Safety Update Reports (PSURs).

Lymphadenopathy

Based on cumulative review of post-marketing data, section 4.8 of the SmPC has been updated to include lymphadenopathy with a frequency rate of "rare" (EMEA/H/C/005737/II/0014).

Tinnitus

The SmPC section 4.8 has been updated to include tinnitus with a frequency rate of "rare" based on imbalance in clinical study results and post-marketing data (EMEA/H/C/005737/II0014).

Diarrhoea

Diarrhoea has been included in the list of ADR at the frequency rate "uncommon" in section 4.8 of the SmPC, this was based on biological plausibility and an observed disproportionality in post-marketing data (EMEA/H/C/005737/II/0014).

Vomiting

Based on reported disproportionality in post-marketing data, a causality between Janssen Covid-19 vaccine and vomiting was established. The SmPC section 4.8 has been updated to include vomiting as an ADR with the frequency "rare" (EMEA/H/C/005737/II/0014).

Hypoesthesia and Paraesthesia

Based on cumulative review of both clinical data and post-marketing data where a disproportionality of paraesthesia and hypoesthesia was observed, the SmPC section 4.8 has been updated to include paraesthesia as an ADR with the frequency rate of "uncommon" and hypoesthesia as an ADR with the frequency rate "rare" (EMEA/H/C/005737/II/0014).

Dizziness

Based on post-marketing data, the SmPC has been updated to include dizziness as an ADR frequency "uncommon" (EMEA/H/C/005737/II/0020).

Adverse Reactions

Adverse Drug Reactions (ADRs) listed in the SmPC, approved 03 August 2021, are provided below. This table includes all updates that have been done from the time of the conditional MA in the EU on 11th of March 2021 up to DLP for this application.

Frequencies were originally calculated based on the Safety Subset of study COV3001. The most common local adverse reaction reported was injection site pain (48.6%). The most common systemic adverse reactions were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). Pyrexia (defined as body temperature $\geq 38^{\circ}$ C) was observed in 9% of participants. Most adverse reactions occurred within 1 to 2 days following vaccination and were mild to moderate in severity and of short duration (1 to 2 days). Adverse drug reactions based on the latest updates to the SmPC [EMEA/H/C/005737/II/0014, submitted on 23 July 2021, approved on 03 September 2021 and including Late Breaking Information from EMEA/H/C/005737/II/0020, submitted 25 August 2021, procedure ongoing] observed during study CV3001 or from post marketing sources are organized by MedDRA System Organ Class (SOC). Frequency categories are shown in Table 5, with ADRs at the time of the initial submission in grey font, and ADRs to be included pending approval in italics.

Of note, following the DLP of this renewal, venous thromboembolism (VTE) has also been added as an ADR in the table with the rare frequency (although not shown in the Table 5).

Table 5 Adverse reactions reported following vaccination with Ad26.COV2.S- Changes since the initial application

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10000 to < 1/1000)	Very Rare (< 1/10000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Lymphadenopathy		
Immune system disorders				Hypersensitivity[a]; urticaria		Anaphylaxis[b] *Immune thrombocytopenia*[c, d]
Nervous system disorders	Headache		Tremor; Paraesthesia *Dizziness*[d]	Hypoaesthesia	Guillain-Barré syndrome	
Ear and labyrinth disorders				Tinnitus		
Vascular disorders					Thrombosis in combination with thrombo-cytopenia[c]	Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders		Cough	Sneezing; oropharyngeal pain			
Gastrointestinal disorders	Nausea		Diarrhoea	Vomiting		
Skin and subcutaneous tissue disorders			Rash; hyperhidrosis			
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Muscular weakness; pain in extremity; back pain			
General disorders and administration site conditions	Fatigue; injection site pain	Pyrexia; injection site erythema; injection site swelling; chills	Asthenia; malaise			

[a] Hypersensitivity refers to allergic reactions of the skin and subcutaneous tissue.
[b] Cases received from an ongoing open-label study in South Africa.
[c] Immune thrombocytopenia has been reported in the post-marketing setting (see section 4.4).
[d] Immune thrombocytopenia and Dizziness added as ADRs in the EMEA/H/C/005737/II/0020, submitted 25 August 2021 (procedure ongoing and therefore outside the reporting period), and included here as *Late Breaking Information, with the ADRs listed in italics.*
* Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).
ADRs listed in the SmPC at the time of the intil cMA are shaded out in grey; new ADRs that have been identified during the reporting period and that are listed in the current SmPC are black font; new ADRs that the MAH is proposing to add to the SmPC pending approval from EMA are in italics and underlined.

Signals Not Confirmed by the MAH During the Reporting Period

- Review of Myocarditis and Pericarditis

In the last MSSR it was concluded that there is currently insufficient data to support for a causal relationship with the Ad26.COV2.S and myocarditis or pericarditis, however, the MAH will continue to monitor this topic closely.

- Review of Blindness

Blindness/visual impairment has been further evaluated in the last two MSSRs and the MAH has presented a cumulative review, based on that information a causal relationship could not be established. The MAH will continue to monitor this topic closely.

- Flare of autoimmune disorders
- Multisystem Inflammatory Syndrome: evaluation currently ongoing

Flare of Autoimmune Disorders and Multisystem Inflammatory Syndrome (MIS) are currently under evaluation.

Significant Changes Made to The Reference Information

The Reference Information (RI) for Ad26.COV2.S, per the initial conditional MA application, is the SmPC.

The SmPC in effect at the start of the period (i.e., at the time of the initial conditional MA) was dated 11 March 2021 and the SmPC in effect at the end of the renewal reporting interval was submitted on 23 July 2021 and approved on 03 September 2021. The SmPC for Ad26.COV2.S was updated numerous times during this reporting period, through to the data lock point (DLP) of this renewal reporting interval (31 July 2021). Table 6 below provides a listing of significant changes to the SmPC during the reporting interval.

Table 6 Significant safety changes to the Ad26.COV2.S Summary of Product Characteristics from c MA (11 March 2021) to 31 July 221

Procedure	Description of Change
Contraindications	
EMA/H/C/5737/II/0010, Approved 09 July 2021	**Addition of Contraindication for Capillary Leak Syndrome** Individuals who have previously experienced episodes of capillary leak syndrome (CLS) (see also Section 4.4).
Warnings and Precautions	
EMA/H/C/5737/IA/0003, Approved 22 April 2021; EMA/H/C/5737/IA/0004, Approved 07 May 2021; EMA/H/C/5737/II/0006/G, CHMP opinion 7 July 2021	**Addition of Thrombosis with thrombocytopenia syndrome (TTS)** A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first 3 weeks following vaccination, and mostly in women under 60 years of age. Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, seizures, mental status changes or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (eg, hematologists, specialists in coagulation) to diagnose and treat this condition. Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with COVID-19 Vaccine Janssen should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.
	Clarification of risk of Thrombocytopenia and coagulation disorders *Risk of bleeding with intramuscular administration* As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.
EMA/H/C/5737/II/0010, Approved 09 July 2021	**Addition of Capillary leak syndrome** Very rare cases of Capillary Leak Syndrome (CLS) have been reported in the first days after vaccination with COVID-19 Vaccine Janssen, in some cases with a fatal outcome. A history of CLS has been reported. CLS is a rare disorder characterized by acute episodes of oedema mainly affecting the limbs, hypotension, haemoconcentration and hypoalbuminaemia. Patients with an acute episode of CLS following vaccination require prompt recognition and treatment. Intensive supportive therapy is usually warranted. Individuals with a known history of CLS should not be vaccinated with this vaccine. See also Section 4.3.

EMA/H/C/5737/II/0012, Approved 23 July 2021	**Addition of Guillain-Barré syndrome** Guillain-Barré syndrome (GBS) has been reported very rarely following vaccination with COVID-19 Vaccine Janssen. Healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes.
Late Breaking Information	
EMEA/H/C/005737/II/0020 Submitted on 25 August 2021, procedure ongoing	**Thrombocytopenia** Request to update the SmPC, Section 4.4. to including a warning/precaution to monitor platelet levels following vaccination with COVID-19 Vaccine Janssen in individuals with a history of ITP. **Addition of Immune thrombocytopenia** Very low platelet levels (<20,000 per µL) have been reported very rarely in the post-marketing setting typically within the first 4 weeks after receiving COVID-19 Vaccine Janssen. Some of these cases occurred in individuals with a history of Immune thrombocytopenia (ITP). Healthcare professionals should assess an individual's relevant medical history prior to administering COVID-19 Vaccine Janssen. If an individual has a history of ITP, discuss the risks and benefits of developing low platelet levels before administering the vaccine. Healthcare professionals should be alert to signs and symptoms of ITP, such as spontaneous bleeding, bruising or petechiae. It is recommended to monitor platelet levels in individuals with a history of ITP following vaccination with COVID-19 Vaccine Janssen. If ITP diagnosis is confirmed, promptly initiate appropriate medical intervention.

Adverse Drug Reactions (ADRs)	
EMA/H/C/5737/IA/0003, Approved 22 April 2021,	Addition of Thrombosis in combination with thrombocytopenia - Frequency category: Very rare (< 1/10,000)
EMA/H/C/5737/II/0010, Approved 09 July 2021	Addition of Capillary leak syndrome - Frequency category: Not known (cannot be estimated from the available data)
EMA/H/C/5737/II/0012, Approved 23 July 2021	Addition of Guillain-Barré syndrome - Frequency category: Very rare (< 1/10,000)
EMEA/H/C/005737/II/0014, Submitted 23 July 2021, Approved 03 September 2021	Addition of the following ADRs based on postmarketing observations: Diarrhoea - frequency category: Uncommon (≥1/1000 to < 1/100) Lymphadenopathy - frequency category: Rare (≥1/10,000 to < 1/1000) Vomiting - frequency category: Rare (≥1/10,000 to < 1/1000) Tinnitus - frequency category: Rare (≥1/10,000 to < 1/1000) Hypoaesthesia - frequency category: Rare (≥1/10,000 to < 1/1000) Paraesthesia - frequency category: Uncommon (≥1/1000 to < 1/100)
Late Breaking Information	
EMEA/H/C/005737/II/0020 Submitted on 25 August 2021, procedure ongoing	Addition of the following ADRs based on postmarketing observations: Dizziness - frequency category: Uncommon (≥1/1000 to < 1/100) Immune Thrombocytopenia - Frequency category: Not known (cannot be estimated from the available data)

Based on updates from the initial version of the SmPC at the time of the cMAA dated 11 March 2021, to the latest version of the SmPC, approved 03 August 2021 (EMEA/H/C/005737/II/0014) and covering the reporting interval up to 31 July 2021.

The following changes to the product information were recommended after the DLP of this renewal:

Venous Thromboembolism (VTE) has been kept under close monitoring by PRAC due to a higher proportion of cases of VTE observed in the vaccinated group compared with the placebo group in the large clinical trial used to authorise COVID-19 Vaccine Janssen. When taking all evidence into account, PRAC concluded that there is a reasonable possibility that VTE is linked to vaccination with Ad26.COV2.S. PRAC therefore recommended adding VTE to the product information of Ad26.COV2.S as a rare side effect (i.e. occurring in less than 1 in 1,000 individuals), together with warnings for healthcare professionals and people taking the vaccine, especially those who may have an increased risk of VTE.

PRAC recommended that transverse myelitis (inflammation in parts of the spinal cord) should be added to the product information as a side effect of Ad26.COV2.S (ongoing procedure). This conclusion is based on worldwide transverse myelitis cases spontaneously reported by 31 August 2021, of which 10 have been assessed to have at least a possible causal relationship with the vaccine, and 1 a probable causal relationship (more than 33 million doses of Ad26.COV2.S were estimated to have been administered worldwide by 31 August 2021). Spontaneously reported cases concern suspected side effects, i.e. medical events that have been observed after vaccination, but which are not necessarily related to or caused by the vaccine. The frequency category is proposed to be 'unknown' because it is generally difficult to robustly estimate side effect frequencies from cases of suspected side effects that have been reported spontaneously by healthcare professionals or patients.

Ad26 platform data

Updated reports presenting the cumulative review of SAEs, pregnancy data, and neuroinflammatory adverse events with the Ad26 platform data were submitted and have/will be evaluated in:

- Procedure EMEA/H/C/005737/REC/19 (cut-off date is 31 Dec 2020 for the AdVac V6.0 database and 21 Dec 2020 for the additional studies in the Janssen Global Safety Database) (closed)
- Procedure EMEA/H/C/005737/REC/34 (cut-off date is 31 July 2021 for the AdVac V7.0 database) (currently assessed).

Current remaining recommendations:

The applicant is recommended to submit, to support the development of future Ad26 vaccines, an updated Advac report integrating the data from the COVID-19 vaccine. Several points to consider in this future report are raised below.

In the AdVac safety database V5, safety data have been provided irrespective of dose level and per subject (cumulating AE after all doses). In further reports, the applicant is recommended to provide the solicited AEs data for dose level $5x10^{10}$ and separately for other dose levels. Data should be presented separately, after dose 1 and after dose 2 (compared to placebo).	EMEA/H/C/005737
High differences of frequency of solicited local and systemic AE have been reported depending of the insert. These differences are difficult to interpret given the confounding effect of several factors which could influence reactogenicity. Overall, the frequency of solicited local and systemic AEs tended to be lower in individuals with pre-existing Ad26 VNA positivity at baseline compared those without pre-existing Ad26 VNA positivity at baseline, but again the independent effect of immunity to the vector is unclear. There were also differences in reactogenicity profile across regions and age categories. In further reports, the applicant should list the factors that could influence reactogenicity and provide local and systemic solicited AE stratified for these factors, to allow for a better	EMEA/H/C/005737

understanding of the independent influence of insert, pre-existing immunity to the vector, and other factors on reactogenicity.	
The frequency of solicited AE local and systemic is generally much lower in West Africa than in other regions (East and Southern Africa, North America, Europe, and Asia), both for the active and placebo groups. Other differences were noted between African and other regions, such as that in the 3 African regions, no consistent difference between groups was observed as in America, Europe, and Asia. Moreover, in Ad26 individuals, the frequency of severe solicited systemic AEs (all, and related solicited systemic AEs) was lowest in East, West and Southern Africa compared to the other 3 regions. Regional differences in safety were already noted in the Zabdeno EPAR. At that time, the applicant argued that cultural differences may explain the differences in reporting rates of AEs across countries and regions. Discrepancies across regions could also reflect differences in terms of pre-existing immunity to Ad26 (higher in Africa) and methodological differences between studies. These discrepancies across regions should be discussed in further reports.	EMEA/H/C/005737
In the AdVac safety database V5, only limited clinical safety data, and brief conclusions have been given for adults ≥60 years, based on data from the RSV vaccine clinical development program. In further reports, the applicant is required to provide an adverse events table by age group (less than 65, between 65-74, 75-84 and 85 and above) and to discuss it.	EMEA/H/C/005737
The MAH should further investigate the limitations of the data pooling methods via additional stratified analyses in the AdVac Safety database report V7.0	EMEA/H/C/005737

3.5. Pharmacovigilance inspections

Pharmacovigilance (PV) system inspections conducted during the reporting period as part of the ongoing EMA Pharmacovigilance Risk Assessment Committee (PRAC) evaluation of the Ad26.COV2.S vaccine are listed below:
During the reporting period for this renewal, 1 sponsor inspection by the Dutch Health and Youth Care Inspectorate took place for the COV3001 clinical trial. None of the findings have a direct impact on the benefit/risk balance for Ad26.COV2.S.

4. Risk management plan

No updated version of the RMP was submitted within this renewal procedure. The MAH has confirmed that the current approved RMP (Version 1.4) which was approved at the time of the initial conditional MA, remains unchanged and applicable at the time of the DLP.

After the DLP of this procedure (31 July 2021), an updated RMP (version 2.2) was submitted to EMA (EMEA/H/C/005737/II/0018) on 3 August 2021. to include the following:

- Thrombocytopenia as an Important Potential Risk following the outcome of the signal of Embolic and thrombotic events (SDA 018.1, EPITT number 19689 procedure No. SDA 018.1) and the opinion of procedure EMEA/H/C/005737/II/0006/G. Following receipt of the PRAC outcome dated 05 August 2021 related to the MSSR covering June 2021 (EMEA/H/C/005737/MEA/014.3), in which the PRAC made the request to update thrombocytopenia to an Important Identified Risk, the MAH response to this request was submitted as a supplementary sequence to ongoing procedure EMEA/H/C/005737/II/0018.

- To propose studies aimed at further characterization of TTS and thrombocytopenia, following the outcome of the signal of Embolic and thrombotic events (SDA 018.1, EPITT number 19689 procedure No. SDA 018.1)
- GBS as Important Identified Risk and update all relevant sections of the RMP accordingly (EMEA/H/C/005737/II/0012)

Initially, the MAH proposed to update the RMP to include thrombocytopenia as an important potential risk. However, after the cut-off date of this renewal the MAH has proposed to re-classify the safety concern of thrombocytopenia (including immune thrombocytopenia) to important identified risk due to additional information regarding ITP (EMEA/H/C/005737/II/018).

A summary of the safety concerns at the start and end of the reporting period is shown in the table below.

Table 7 Summary of safety concerns at the start and end of the reporting period

	Approved EU-RMP v 1.4	**EU-RMP v2.2, submitted 03 August 2021**
Important Identified Risks	– Anaphylaxis	– Anaphylaxis – Thrombosis with thrombocytopenia syndrome (TTS)[1] – Guillain-Barré syndrome[2]
Important Potential Risks	– Venous Thromboembolism – Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	– Venous Thromboembolism – Thrombocytopenia[3] – Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (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 (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) – Interaction with other vaccines – Long-term safety	No change in v2.2

1. The list of safety concerns in the EU-RMP has been amended to include TTS as an Important Identified Risk, based on spontaneous/solicited post-marketing reports of severe and very rare cases of thrombosis in combination with thrombocytopenia, including venous thrombosis such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, as well as arterial thrombosis (EMEA/H/C/005737/IA/0004 and EMEA/H/C/005737/II/0006/G)
2. The list of safety concerns in the EU-RMP has been updated to include GBS as an Important Identified Risk, following the procedure EMEA/H/C/005737/II/0012 in which information was included up to the DLP of 02 July 2021 for clinical trial GBS cases and 30 June 2021 for postmarketing GBS cases.
3. As requested in the final assessment report for procedure number EMEA/H/C/005737/II/0006/G that was shared with the MAH on 08 July 2021, the list of safety concerns in the EU-RMP has been updated to include thrombocytopenia as an Important Potential Risk.

5. Changes to the Product Information

No changes to the Product Information (PI) are introduced with this renewal procedure.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, COVID-19 Vaccine Janssen (adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein) is included in the additional monitoring list as:

- It is approved under a conditional marketing authorisation;
- It has SOBs which have not still been fulfilled.

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.

At time of approval of the conditional marketing authorisation in March 2021, the following quality-related specific obligation was included in Annex II.

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

At the time of approval of the conditional marketing authorisation in March 2021, this SOB only referred to the Catalent Bloomington (USA) Finished Product manufacturing site. In the meantime, the MAH has provided the remaining validation and comparability data for the Catalent Bloomington site as requested in this SOB. The data have been assessed and were found acceptable. Accordingly, the specific obligation related to the Catalent Bloomington site can be considered as fulfilled.

However, this SOB was afterwards also applied to 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), Merck Sharp & Dohme West Point (USA) and Sanofi Pasteur Marcy l'Etoile (France). These manufacturing sites were also conditionally approved via variation procedures with the specific obligation to provide additional validation and comparability data.

For the IDT Biologika (Germany) and Aspen (South-Africa) sites, the remaining validation and comparability data have also been provided. The data have been assessed and were found acceptable. Accordingly, the specific obligation related to the IDT Biologika (Germany) and Aspen (South-Africa) sites can also be considered as fulfilled.

For the other manufacturing sites (Catalent Anagni Italy, Sanofi Pasteur Marcy l'Etoile France and Merck Sharp & Dohme West Point USA), the assessment of the data as requested by SOB is still ongoing. For some of these sites, interim reports have been provided with partial and/or preliminary

data which were all found acceptable thus far.

All interim reports and final reports related to the FP SOB for the various manufacturing sites have been submitted before the specific due date for each data package (as approved in the conditional MA and the respective variation reports).

In addition, a SOB related to the active substance was added following Variation IB/11 to upgraded the AS facility at Janssen Biologics Leiden (Netherlands). Please refer to Table 2 for a detailed overview of the quality SOBs. Interim reports related to this SOB have been submitted and evaluated, the final report has been submitted and the assessment of type II/37 is ongoing.

An overview of the conditions and specific obligations submitted since the granting of marketing authorisation and prior to 1st September 2021 is presented below.

Description	Procedural number	Status
SO: In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional comparability and validation data.		
From IB/011: 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)** **b) A second interim report containing including RCA results for PPQ batches 2 and 3, complete**	EMEA/H/C/005737/IB/0011	**The first report has been submitted on 28/07/2021 with assessment concluded on 16.9.2021.** **The second report has been submitted on 10/08/2021 with assessment concluded on 11.11.2021** **The final report has been submitted via type II variation on 30.11.2021 with assessment ongoing and for conclusion on 10.02.2022**

Description	Procedural number	Status
PPQ data and tier 1 comparability data. (by 13 August 2021) **c) A final report with tier 2 comparability data. (by 30 November 2021)**		
SO: In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.		
<u>From initial cMA:</u> The applicant 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.**	EMEA/H/C/005737/II/0017	**a) The interim report has been submitted on 30/03/2021 and was approved on 24/06/2021.** **b) The final report has been submitted on 3/08/2021 via type II variation with assessment concluded on 21.10.2021.**
<u>From initial cMA:</u> In addition, since the analytical method transfer from the US to EU is ongoing, Annex II of the opinion will include: *'In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 30 June 2021. Implementation of EU*	EMEA/H/C/005737/IA/0009	**Type IA variation to remove ex-EU release testing activities was submitted on 24/06/2021 and approved on 25/06/2021 (please note there was a subsequent variation submitted in relation to this - see EMEA/H/C/005737/IB/0002/G on page 3).**

based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 30 June 2021 at the latest, in line with the agreed plan for this transfer of testing.'		
From IB/001/G: The MAH should provide post-approval as part of a specific obligation the process validation data (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. (due date 19/04/2021)** **b) A second report with initial PPQ data and tier 1 comparability. (due date 31/05/2021)** **c) A final report with all remaining PPQ results and tier 2 data. (due date 30/09/2021)**	EMEA/H/C/005737/IB/0001/G	**a) The first report has been submitted on 19/04/2021 and was approved on 20/05/2021.** **b) The second report has been submitted on 27/05/2021 and approved on 19/08/2021.** **c) The final report has been submitted on 29/09/2021 via type II variation and approved on 16.12.2021.**
From IB/002/G: 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:	EMEA/H/C/005737/IB/0002/G	**a) The first report has been submitted on 16/04/2021 and was approved on 20/05/2021** **b) The final report has been submitted via type II variation on 12/05/2021 and**

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).**		**was approved on 24/06/2021**
From IB/002/G: In addition, since the analytical method transfer from the US to EU is ongoing, Annex II of the opinion will include: *'In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 July 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 July 2021 at the latest, in line with the agreed plan for this transfer of testing.'*	EMEA/H/C/005737/IB/0002/G	**A type IA variation to remove ex-EU release testing activities has been submitted on 29/07/2021 and approved on 30/07/2021 (please note there was a previous variation submitted in relation to this - see EMEA/H/C/005737/IA/0009 on page 1.)**
From IB/008: 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	EMEA/H/C/005737/IB/0008	**a) The first report including CoA for PPQ batch 3 has been submitted on 16/07/2021 and was approved on 22/07/2021.**

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 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. (due date: 16/07/2021)** **b) A second report with initial PPQ data and tier 1 comparability. (due date: 31/08/2021)** **c) A final report with all remaining PPQ results and tier 2 data. (due date: 31/10/2021)**		**b) and c)** **A type IB variation including revised due dates was submitted on 16/07/2021 and approved on 22/07/2021 (the revised due dates are provided in the row below).** **<u>Please note</u> that because an out-of-specification (OOS) result was obtained for PPQ batch 2 - a CoA for PPQ batch 3 has been submitted 16/7/2021 and CoAs for PPQ batches 4 and 5 have been submitted 24/8/2021 with all batches considered releasable by EMA (3 consecutive PPQ batches)**
<u>From IB/013:</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 sites. The following 3 reports are expected:	EMEA/H/C/005737/IB/0013	**Please note, as mentioned above, the revised due dates as confirmed by the type IB variation are provided for a), b) and c) in the far-left column of this row.**

a) A first report containing CoAs with the QC release results of the pending PPQ batch. This report should be provided as soon as possible and in any case before this pending batch is released to the market. It is also recommended to include in this interim report a summary of the investigation on the OOS of the bioburden IPC test observed for the 2nd PPQ lot. (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: 31/03/2022)**		
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:**	EMEA/H/C/005737/IB/25/G	**Pending**

31/05/2022)		
<u>From IB/36:</u> 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. 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: 30/06/2022)**	EMEA/H/C/005737/IB/36	**Pending**

Taken together, whereas this SOB relates to different finished product 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 this SOB ("*In order to confirm the consistency of the*

finished product manufacturing process, 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/indicating the validates status of the process. For the Catalent Bloomington (USA) site, the Aspen south Africa site and the IDT Biologika (Germany) site, this SOB can be considered as fulfilled. For the other site, assessment is still ongoing.

In addition, a Specific Obligation related to the active substance was added following Variation IB/11 to upgrade the AS facility at Janssen Biologics Leiden (Netherlands). Please refer to Table 2 for a detailed overview of the quality SOBs. Interim reports related to this SOB have been submitted and evaluated, the final report has been submitted and the assessment of type II/37 is ongoing.

It should be noted that these SOBs may be applied to future variations as well (for additional manufacturing sites).

As such, since the assessment of AS and FP related SOBs is still ongoing for several manufacturing sites and since these SOBs may also be applied to future variations to implement additional manufacturing sites, these overarching SOBs (applicable to various manufacturing sites) cannot be considered closed for the time being.

Clinical-related SOBs

The status of the clinical SOBs is provided below:

Description	**Procedural number**	**Status**
Clinical Specific Obligations: 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.		
From initial conditional MA: The MAH should submit the final Clinical Study Report (CSR) for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	N/A	As informed during the meeting held on 17 June 2021, final analysis (end of double-blind phase) on COV3001 will not be available for submission in the renewal. Given that a submission of data on COV3001 is expected in Q42021, as agreed during the meeting held on 17 June, the annual renewal will therefore focus on information related to accrual, conduct of the study and MAH conclusion on feasibility of concluding study on time only.
From initial conditional MA: Submission of final CSR for VAC31518COV3001 by 31 December 2023	N/A	Final CSR (including long-term follow-up) is on track for submission by 31 December 2023. The CSR for the final analysis of the double-blind phase is planned in the last quarter of 2021.

Updated list of specific obligations (SOBs)

In the framework of a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the consistency of the active substance manufacturing process, the applicant should provide additional validation and comparability data	30 November 2021 Interim report: 03 August 2021 Interim report: 13 August 2021
In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data	30 June 2022 Interim report: 15 December 2021 Interim report: 20 December 2021 Interim report: 31 January 2022 Interim report: 31 January 2022
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 COVID-19 Vaccine Janssen in the approved indication.

Furthermore, the data collected as part of the specific obligation(s) for COVID-19 Vaccine Janssen during the period covered by this annual renewal continue to support its positive benefit-risk balance in the approved indication.

Favourable effects

As stated in the EPAR of the conditional marketing authorisation (CMA) for COVID-19 Vaccine Janssen, the cMA was granted based on data of the pivotal Phase 3 trial COV3001 and supporting studies. No new efficacy or immunogenicity data are submitted in the renewal application.

Efficacy of Ad26.COV2.S for the co-primary endpoint 'moderate to severe/critical COVID-19' with an onset from Day 14 after vaccination was 66.9% (adjusted 95% CI: 59.03; 73.40) over a median follow up time of 58.0 days, in seronegative individuals. For the co-primary endpoint 'moderate to severe/critical COVID-19' with an onset from Day 28 after vaccination, efficacy was 66.1% (adjusted 95% CI: 55.01; 74.80) over the same period, in seronegative individuals. The primary objective was met for both co-primary endpoints since the lower limit (LL) of the 95% CI of vaccine efficacy were above the pre-specified limit of 30%.

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 76.7% (adjusted 95% CI: 54.56; 89.09) over a median follow up of 58 days, in SARS-COV-2 seronegative subjects. Of the 66 vs. 193 primary endpoint cases with an onset at least 28 days after vaccination in the vaccine vs. placebo group respectively, 5 (8%) vs. 34 (18%) were classified as severe. VE against severe disease was estimated at 85.4% (adjusted 95% CI: 54.15; 96.90) over the same follow-up period in 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.

There were 2 vs. 8 cases of molecularly confirmed COVID-19 requiring hospitalisation at least 14 days after vaccination in the active vs. placebo group, respectively. The finding was supported by post-hoc analyses which identified 2 vs. 29 cases of all COVID-19 related hospitalisations by implementing a broader search based on all available information (including SAE forms) in the extended data set, i.e. all COVID-19 cases with a positive PCR result, including all cases from a local laboratory result not yet confirmed by the central laboratory at the time of the analysis.

In participants ≥65 years, based on the primary endpoint, efficacy was 82.4% (95% CI: 63.90; 92.38) after 14 days post-vaccination and 74.0% (95% CI: 34.40; 91.35) after 28 days post-vaccination.

Uncertainties and limitations about favourable effects

No new uncertainties and limitations have emerged since no new efficacy or immunogenicity data have been submitted since the cMA. As described in the EPAR, the main uncertainties remain the unknown duration of protection and efficacy in risk groups, e.g. immunocompromised persons due to condition or immunosuppressive therapies, frail individuals, individuals with uncontrolled underlying disease or with several underlying diseases. Whether efficacy is higher against severe cases compared to all symptomatic cases is not confirmed yet, but there is a trend in that direction. Another uncertainty is vaccine efficacy against variants of concern. Efficacy was demonstrated in South Africa where the South African variant 20H/501Y.V2 was predominant. Efficacy was demonstrated in Brazil, but there was no predominant variant in Brazil. Two third of the cases may be attributable to the P.2 lineage. Spike sequence data were available for only 70% of the cases and a higher proportion of samples were sequenced in the placebo group as compared to the vaccine group, which could lead to biases. An analysis of vaccine efficacy per SARS-CoV-2 variant is planned upon completion of the sequencing. The extent and the onset of cross-protection against other relevant circulating or newly emerging strains of SARS-CoV-2 is unknown and should be investigated post-authorisation.

Unfavourable effects

Data from clinical studies

At the time of the c MA, the assessment of Ad26.COV2.S safety was based on the Phase 3 study COV3001 (up to the cut-off date of 22 January 2021), comprising 43,783 participants who received either a single dose of Ad26.COV2.S at 5x1010 vp (21,895 adults) or placebo (21,888 adults) (FAS). Reactogenicity data were collected in a subset of 6,736 participants who received either vaccine (3,356 adults) or placebo (3,380 adults) (Safety subset). Information on unsolicited AEs was collected for 28 days after vaccination, information on AESIs and SAEs is collected for the entire study duration. At the time of the primary analysis, the median follow-up after vaccination was 58 days in both groups.

Any solicited local and systemic AEs were reported more frequently in Ad26.COV2.S than in the control group (66% and 41.9% of evaluated participants respectively, within the first 7 days following injection). The most frequently reported solicited local AE after Ad26.COV2.S vaccination was injection site pain (48.7% vs. 16.7%, respectively). The most frequently reported solicited systemic AEs were headache (39% in Ad26.COV2.S group vs. 23.8% in the placebo group), fatigue (38.3% vs. 21.6%, respectively), and myalgia (33.2% vs. 12.8%). Pyrexia was reported in 9.0% participants in the Ad26.COV2.S group (vs. 0.6% of participants in the placebo group). Most solicited AEs were transient and self-limited. Overall, the median duration of the selected solicited AEs was similar in both groups

(1 to 2 days after vaccination), and also the median time to onset (within 1 to 3 days after vaccination). Solicited adverse events were mainly grade 1 or 2. The frequency of Grade 3 solicited AEs was low overall, but higher in participants in the Ad26.COV2.S group (2.2%) compared to participants in the placebo group (0.7%). There was no grade 4 solicited AEs.

In the safety subset, the frequency of unsolicited AEs reported was low and similar in both (13.1% vs. 12%, respectively). Unsolicited AEs were largely consistent with solicited AEs observed following vaccination, such as headache, fatigue, myalgia, and vaccination site pain. The most frequent unsolicited ADRs that were not recorded as solicited AEs were chills, arthralgia, malaise, asthenia, muscular weakness and pain in extremity. Most reported unsolicited AEs were Grade 1 or Grade 2 in severity. There was a similar frequency of participants with unsolicited AEs of at least Grade 3 in both groups. The frequency of unsolicited AEs that were considered related to vaccination was higher in participants in the Ad26.COV2.S group as compared to placebo (7.2% vs. 4.6%, respectively).

Up to the cut-off date, in the FAS, the same frequency of subjects reported at least one treatment emergent AESI in both groups (0.6%). Few reported AESIs were assessed as related (0.2% vs. 0.1%, respectively).

Fewer deaths were observed in the Ad26.COV.2.S group (3, none confirmed to be associated with COVID-19) compared to the placebo group (16, including 6 confirmed to be associated with COVID-19). In the FAS, 0.4% subjects in the Ad26.COV2.S group and 0.6% subjects in the placebo group reported 1 or more non-fatal SAEs. However, a similar frequency of subjects reported SAEs not associated with COVID-19 in both groups (0.4%). Of the 227 SAEs reported, 7 SAEs (reported for 7 participants) in the Ad26.COV2.S group and 3 SAEs (reported for 2 participants) in the placebo group were considered to be possibly related to the vaccination. The reported SAEs considered related by the investigator for the Ad26.COV2.S vaccine were Guillain-Barré syndrome, pericarditis, brachial radiculitis, post-vaccination syndrome, Type IV hypersensitivity and 2 cases of facial paralysis.

Overall, the safety profile of the vaccine was similar independently of the subgroups. However, reactogenicity was milder and less frequent in older adults aged ≥65 years compared to the younger adults aged ≥18 to 64. Higher reactogenicity was reported in females compared to males (although both subgroups had a similar median age).

In study COV3001, the most frequently reported 'non-anaphylactic allergic reactions' were rash (24 vs. 16; 10 related vs. 6 related, respectively), urticaria (8 vs. 3; 3 related vs. none, respectively), and hypersensitivity (6 in the vaccine group including 1 related, 4 in the placebo group of which none related). Moreover, since the data lock, a SUSAR was reported which meet the Brighton Collaboration case definition criteria for anaphylaxis from an ongoing study in South Africa. Hypersensitivity, rash, urticaria, and anaphylaxis are considered at least possibly causally related to vaccination and have thus been listed as ADRs in the SmPC. Anaphylaxis is also considered as an important identified risk in the RMP.

Regarding immune-mediated neurological disorders, there was 1 subject with Guillain-Barré syndrome in each group (1 possibly related grade 4 SAE in the Ad26.COV2.S group with a plausible temporal relationship, 1 non-related SAE in placebo group). The risk of Guillain-Barré syndrome is included in the list of AESIs taken in consideration for routine and additional pharmacovigilance activities.

There were 3 cases of Bell's palsy (facial paralysis) in the Ad26.COV2.S group (2 SAE considered as possibly related SAEs by the investigator, but not related by the Sponsor; and 1 non-related AE) compared with 2 cases in the placebo group (non-related). Based on data from reported events, a causal relationship between Ad26.COV2.S vaccination and Bell's palsy could not be confirmed nor ruled out (at least 2 cases possibly related to the vaccine). Bell's palsy is included in the list of AESIs subject

to routine and additional pharmacovigilance activities, but not in the SmPC as there is no clear imbalance vs. placebo.

A numerical imbalance was observed for the venous thrombotic events with 11 subjects in the Ad26.COV2.S group (6 DVT events, 4 pulmonary embolism, 1 transverse sinus thrombosis (later classified as TTS); 6 SAEs; 8 events occurred within 28 days following vaccination) vs. 4 in the placebo group (2 DVT events, 1 pulmonary embolism, 1 thrombosed haemorrhoid; 2 SAEs; all within 28 days of vaccination). Two of these cases were considered related to the study vaccine by the investigator (1 in each group). However, as the majority of the participants had underlying medical conditions (such as obesity, hypothyroidism, diabetes) that could have contributed to the thrombotic and thromboembolic events, the causal relationship between Ad26.COV2.S vaccination and venous thrombotic events was not shown. Venous thromboembolism has been included as an important potential risk in the list of safety concerns of the RMP.

Asthma was reported for 7 participants in the Ad26.COV2.S group versus 1 participant in the placebo group, although most were unrelated to study treatment. In the Respiratory, thoracic and mediastinal disorders, 10 subjects reported 10 SAEs in the Ad26.COV2.S group (3 Pulmonary embolism, 2 Dyspnoea, 2 Hypoxia, 1 Chronic obstructive pulmonary disease, 1 Pleural effusion, 1 Pneumothorax spontaneous) compared to 4 subjects reporting 6 SAEs in the placebo group (Pulmonary embolism, Dyspnoea, Cough, Oropharyngeal pain, Respiratory distress, Respiratory failure). Although the causality is not clear, because there is an imbalance in the number of cases vs. placebo, the risk of exacerbation of chronic pulmonary disorders (i.e. asthma and COPD) might be further monitored in the planned PASS as an AESI (pending feasibility assessment that will be included in the draft protocol).

Post-marketing data

Since the initial safety assessment at the time of the conditional MA, additional information became available through routine safety pharmacovigilance activities (such as signal detection, MSSRs) for which the results were reflected in updates of the EU-RMPs and SmPC during the reporting period.

Important identified/potential risks:

Thrombosis with Thrombocytopenia Syndrome (TTS): The EUPI has been updated to include TTS as an adverse reaction and text was added to Section 4.4 Special warnings and precautions for use, and the EU-RMP has been amended to include TTS as an Important Identified Risk, based on spontaneous/solicited post-marketing reports of severe and very rare cases of thrombosis in combination with thrombocytopenia, including venous thrombosis such as CVST, splanchnic vein thrombosis, as well as arterial thrombosis (EMEA/H/C/005737/IA/0004 and EMEA/H/C/005737/II/0006/G).

Guillain-Barré syndrome (GBS): The SmPC, Section 4.8 Undesirable effects was updated to include GBS as an ADR following vaccination with Ad26.COV2.S, with frequency grouping "very rare" and given the seriousness of the event. Text was added to Section 4.4 Special warnings and precautions for use, to advise that healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes (EMEA/H/C/005737/II/0012). The list of safety concerns in the EU-RMP has been updated in version 2.2 (submitted 03 August 2021) to include GBS as an Important Identified Risk, following the assessment of the data submitted as part of the procedure EMEA/H/C/005737/II/0012.

Thrombocytopenia / Immune Thrombocytopenia: In line with recommendations from the PRAC, received on 05 August 2021 in response to the MSSR (EMEA/H/C/005737/MEA/014.3), the MAH has submitted a Type II variation on August 25, 2021 (EMEA/H/C/005737/II/0020) to update the SmPC, to include ITP as an ADR with a frequency "not known" (Section 4.8 of the SmPC). A warning and precaution statement relating to observation of very low platelet levels following vaccination with

Ad26.COV2.S is proposed to be included in Section 4.4 of the SmPC. A second statement was added on healthcare professionals assessing an individual's relevant medical history. A third statement was included on alerting of healthcare professionals to signs and symptoms of ITP, and a recommendation was included to monitor platelet levels in patients with a history of ITP.

As an outcome of the June 2021 MSSR assessment (EMEA/H/C/005737/MEA/014.3), the PRAC requested to include thrombocytopenia as an Important Identified Risk. Discussion on the re-classification of risk of thrombocytopenia and ITP is currently ongoing (EMEA/H/C/005737/II/0018).

Other new recognized ADRs:

Capillary leak syndrome (CLS): Considering the occurrence of a new flare of CLS, with fatal outcome, in an individual with a medical history of CLS, in close temporal association with administration of Ad26.COV2.S, a causal role of the vaccine in severe exacerbations of CLS in individuals with a medical history of CLS cannot be excluded. The EUPI has been updated to include a contraindication (Section 4.3) for individuals who have previously experienced episodes of CLS; CLS was added to Section 4.4 Special warnings and precautions for use and to Section 4.8 Undesirable effects as an ADR with the frequency category "Not known (cannot be estimated from the available data)" (EMEA/H/C/005737/II/0010). The MAH continues to monitor CLS and includes an interval review in the MSSRs.

Lymphadenopathy: Based on the cumulative review of post-marketing reports of lymphadenopathy captured in the GMS database and scientific literature, there is a reasonable plausibility of an association between the occurrence of lymphadenopathy and the use of the Ad26.COV2.S vaccine. The MAH has submitted a Type II variation on 23 July 2021 (EMEA/H/C/005737/II/0014), which was approved on 03 September 2021, and in which updates are made to the SmPC Section 4.8 and the PL, Section 4, to include lymphadenopathy as an ADR, with a frequency " rare."

Tinnitus: Based on the imbalance from the clinical study database, and available post marketing data, there is sufficient evidence to conclude on at least a reasonable possibility for a causal relationship between tinnitus and the Ad26.COV2.S vaccine. A Type II variation (EMEA/H/C/005737/II0014) was submitted on 23 July 2021 and approved on 03 September 2021 to include tinnitus as an ADR to Section 4.8 of the SmPC with a frequency "rare". As agreed with EMA, the discussion and presentation of available data with regards to further characterization of tinnitus will be handled as part of the upcoming MSSRs planned for submission on 15 September 2021.

Diarrhoea: The EUPI has now been updated to include diarrhoea as an ADR, based on biological plausibility and disproportionate post marketing reporting. A Type II variation was submitted on 23 July 2021, approved 03 September 2021 (EMEA/H/C/005737/II/0014) to update the SmPC Section 4.8 to include diarrhoea as an ADR with a frequency "uncommon."

Vomiting: On the basis of the disproportionality of post marketing reporting of vomiting and evidence of causality, the MAH has submitted an EU SmPC Type II variation filed on 23 July 2021 and approved 03 September 2021 (EMEA/H/C/005737/II/0014) to update the SmPC Section 4.8, to include vomiting as an ADR, with a frequency "rare."

Hypoesthesia and Paraesthesia: Based on the disproportionality of post marketing reporting of paraesthesia and hypoaesthesia and evidence of causality, the MAH has submitted an EU SmPC Type II variation filed on 23 July 2021 and approved 3 September 2021, in which it proposes to update the SmPC Section 4.8, to include paraesthesia as an ADR with a frequency rate of "uncommon" and hypoaesthesia as an ADR with a frequency "rare."

Dizziness: Based on disproportionate reporting in the post marketing setting, the MAH has submitted a Type II variation (EMEA/H/C/005737/II/0020) with a proposal to update the EUPI to include dizziness in the list of adverse reactions in Section 4.8 of the SmPC.

Venous Thromboembolism: VTE has been kept under close monitoring by PRAC due to a higher proportion of cases of VTE observed in the vaccinated group compared with the placebo group in the large clinical trial used to authorise COVID-19 Vaccine Janssen. When taking all evidence into account, PRAC concluded that there is a reasonable possibility that VTE is linked to vaccination with COVID-19 Vaccine Janssen. PRAC therefore recommended adding VTE to the product information of COVID-19 Vaccine Janssen as a rare side effect (i.e. occurring in less than 1 in 1,000 individuals), together with warnings for healthcare professionals and people taking the vaccine, especially those who may have an increased risk of VTE (EMEA/H/C/005737/MEA/032). The RMP should be updated at the next regulatory opportunity with upgrading of 'venous thromboembolism' from important potential risk to important identified risk. The MAH's proposal for further characterisation of VTE should also be addressed in an upcoming submission.

Transverse myelitis (procedure ongoing): PRAC recommended that transverse myelitis (inflammation in parts of the spinal cord) should be added to the product information as a side effect of COVID-19 Vaccine Janssen (with a frequency of not known). This conclusion is based on worldwide transverse myelitis cases spontaneously reported by 31 August 2021, of which 10 have been assessed to have at least a possible causal relationship with the vaccine, and 1 a probable causal relationship (more than 33 million doses of COVID-19 Vaccine Janssen were estimated to have been administered worldwide by 31 August 2021).

Evaluations of the unfavourable effects Multisystem Inflammatory Syndrome and Rhabdomyolysis are ongoing.

Uncertainties and limitations about unfavourable effects

Based on the post-marketing safety data submitted which have emerged in the reporting interval, and given that the clinical SOB has not been fulfilled yet (final CSR COV3001 due by December 2023), the uncertainties about unfavourable effects remain identical to the initial assessment, as described in the EPAR. These uncertainties are mainly related to long term-safety, co-administration with other vaccines and safety in specific risk groups (e.g. pregnant women, immunocompromised individuals, frail patients with comorbidities). The RMP contains additional pharmacovigilance activities to further characterise these uncertainties.

Of note, in the initial conditional MA application, the cumulative review of SAEs, pregnancy data, and neuroinflammatory adverse events with the Ad26 platform data (AdVac V5.0 database) have been assessed through the cut-off date of 21 Dec 2020. The data through the 31 Dec 2020 were assessed since the initial conditional MA (EMEA/H/C/005737/REC/19: AdVac V6.0 database) but didn't change the conclusions above. The data through the 31 July 2021 are currently assessed (EMEA/H/C/005737/REC/34: AdVac V7.0 database).

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Despite increasing numbers of vaccinated subjects, the ongoing SARS-CoV-2 pandemic remains a public health issue of international concern. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S has demonstrated high efficacy against severe/critical disease caused by SARS-CoV-2 and protection against COVID-19 related hospitalization and death in the trials that lead to MA. There is no new efficacy data available since MA.

As of 31 July 2021, over 25.7 million doses of the Ad26.COV2.S vaccine have been administered (CDC 2021, ECDC 2021, KDCA 2021). Increasing experience based on spontaneous/solicited post-marketing reporting of adverse events, have led to the identification of new, some serious, adverse events/reactions (including new recognized ADRs in currently published SmPC: TTS, GBS, CLS, lymphadenopathy, paraesthesia and hypoesthesia, dizziness, diarrhoea, vomiting, and tinnitus, VTE, ITP and transverse myelitis which is recommended to be included in ADR table in ongoing procedure) for which causality with the Ad26.COV2.S vaccine has been concluded, based on the available data. These risks occur very infrequently, are adequately monitored and do not outweigh the significant benefits of single-dose vaccination with Ad26.COV2.S in controlling the global pandemic. Potential safety concerns will continue to be monitored.

Balance of benefits and risks

Taking the new safety information into account since approval of the conditional MA up to 31 July 2021, and late breaking information, as presented in the Clinical Overview Addendum, the overall benefit-risk assessment remains favourable for Ad26.COV2.S when used as recommended in the currently approved indication of active immunization to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age.

7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the marketing authorisation holder has complied with the specific obligations and the benefit-risk balance for COVID-19 Vaccine Janssen in its approved indication(s) (please refer to the Summary of Product Characteristics) continues to be favourable and therefore the renewal of the conditional marketing authorisation is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

The renewal requires no amendments to the terms of the marketing authorisation.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific obligations to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the consistency of the active substance (AS) manufacturing process, the MAH should provide additional comparability and validation data.	30 November 2021
In order to confirm the consistency of the finished product (FP) manufacturing process, the applicant should provide additional validation and comparability data.	30 June 2022
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

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.