



RECOMMENDATION FOR AN EMERGENCY USE LISTING OF COVID-19 VACCINE JANSSEN SUBMITTED BY Janssen – Cilag International N. V. (Belgium)

Abstract

The active ingredient of COVID-19 Vaccine Janssen, also known as Ad26.COVS-2 (recombinant), is a recombinant adenoviral vector that contains the sequence that encodes the spike protein (S) of the SARS-CoV-2 virus. After administration, the replication incompetent adenoviral particles will infect cells and the sequence encoding the SARS-CoV-2 Spike protein will be transcribed into mRNA and subsequently translated into SARS-CoV-2 Spike protein which will serve as antigen to trigger an immune response. The adenoviral particle contains the coding sequence of the SARS-CoV-2 Spike protein as an integral part of the genome of the adenoviral construct.

The applicant, Janssen – Cilag International N. V. (Belgium) (Janssen) has used the AdVac® vector platform considering the substantial nonclinical and clinical evidence from Janssen's other vaccine development programs that also make use of Ad26 (e.g., Ebola vaccine Zabdeno®, and candidate vaccines against Zika, HIV and respiratory syncytial virus).

COVID-19 Vaccine Janssen is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

The use of COVID-19 Vaccine Janssen under the current emergency scenario was approved on 11 March 2021 by the European Medicines Agency (EMA). The vaccine is endorsed by other regulatory authorities (e.g., the Food and Drug Administration of the United States of America and Health Canada).

This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).

1 Introduction

1.1 Background

The current COVID-19 pandemic is unprecedented in the 21st century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

Scientists around the world on COVID-19 met at the World Health Organization's Geneva headquarters on 11–12 February 2020¹ to assess what is known about the new severe acute respiratory coronavirus - 2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic.

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint² aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

1.2 COVID-19 vaccines

Shortly after SARS-CoV emerged at the turn of the 21st century, the spike (S) protein (particularly in its native conformation) was identified as the immunodominant antigen of the virus³. Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease⁴.

The current global COVID-19 public health emergency underscores the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit - risk approach.

¹ <https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research>

² <https://apps.who.int/blueprint-brochure/>

³ Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. *Nat Rev Microbiol.* 2009;7(3):226-236.

⁴ Tseng CT, Sbrana E, Iwata-Yoshikawa N, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PLoS One.* 2012;7(4):e35421.

The information available on COVID-19 candidate vaccines⁵ and the new coronavirus (nCoV) epidemiology is closely monitored. The various platform technologies that are developed, based on nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g., MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus, are reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials.

During the past year, there was an unprecedented global effort to develop safe and effective vaccines against COVID-19. These vaccines represent some of the most important tools in ending the pandemic, when combined with proven public health and social measures. Very encouraging results on the safety and efficacy of candidate vaccines have been reported for several candidates. However, the current epidemiological scenario is becoming increasingly complicated with the surge of virus variants due to mutations associated with increased viral transmission and in some cases neutralizing antibody escape. These variants make effective changes in the virus's 'Spike' protein, which the virus uses to enter human cells and some of these variants are posing real challenges for vaccine's efficacy.

In this complex scenario, vaccines that could exert protective immunity after a single dose are preferred.

1.2.1 The Janssen Covid-19 vaccine

The recombinant Ad26 vector (Ad26.COVS) is replication incompetent in human cells due to deletions in the E1 gene. In addition to this genomic deletion, a part of the E3 gene region has been removed to create sufficient space in the viral genome for the insertion of foreign antigens.

The Ad26.COVS vector contains a transgene which encodes a modified full-length SARS-CoV-2 spike protein. The wild-type full-length S gene information was obtained from a SARS-CoV-2 clinical isolate. The production of the recombinant vector expressing the S antigen uses Janssen proprietary cell line (PER.C6 TetR cells). Following administration, the Spike protein is expressed and stimulates an adaptive humoral and cellular immune response.

1.3 Emergency Use Listing

The Emergency Use Listing (EUL) is a time limited risk-benefit assessment for emergency use of vaccines, medicines and in vitro diagnostics during a PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the applicant is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for emergency use following a robust scientific risk benefit assessment. However, each WHO Member States has the sole prerogative to allow the emergency use of a product under an EUL within their country.

⁵ <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

2 Assessment process

Covid-19 Vaccine Janssen is manufactured using different manufacturing nodes in the United States of America (USA) and Europe. The WHO EUL application was submitted by Janssen - Cilag International N.V., Beerse, Belgium. Vaccine batches will be released by Janssen Biologics B.V., Leiden, The Netherlands.

The dossier prepared by Janssen to support the EUL application was submitted to WHO on a rolling submission, following the same procedure as EMA. WHO experts participated in meetings organized by both EMA's Pandemic Task Force (COVID-ETF) and the EMA Committee for Medicinal Products for Human Use (CHMP).

The PEG consisted of several different experts. One focal person was designated by WHO for the quality review and one for the non-clinical and clinical assessment (including Risk Management Plan (RMP)). Clinical reviewers from the roster of experts of the WHO Prequalification unit, as well as reviewers from National Regulatory Authorities (NRA) from different regions, were part of the assessment team. The reviewers were designated to cover the non-clinical, clinical and RMP evaluation of the submission.

The WHO prequalification procedure includes provision for a streamlined (or abbreviated) assessment procedure. The aim of this abbreviated assessment⁶ is to increase efficiencies, avoid duplication of efforts and reduce the time to assess a product by focusing on aspects where WHO prequalification brings added value. The abbreviated approach applies to the prequalification of vaccines that have been licensed by selected eligible NRAs willing to share information with WHO through a collaboration agreement.

The approach described above may be used to assess vaccines during public health emergencies following the EUL procedure. As EMA is the NRA of record for this vaccine, WHO conducted an abbreviated procedure of the dossier relying on the assessment done by the EMA. The WHO review focusses on the data available for use in LMIC.

The PEG's report was prepared for deliberation and recommendation by the TAG, allowing for a WHO recommendation shortly after the CHMP issues a conditional Marketing Authorization.

3 Scientific Review

3.1 Quality Overview

The applicant for Covid-19 Vaccine Janssen, provided information of the different nodes that are involved in the manufacturing of the vaccine. This includes sites in the USA and Europe, responsible to produce the Drug Substance (DS) and Drug Product (DP). Janssen had submitted to WHO the same dossier as to EMA. The EMA ETF will deliberate on 8 March. The EMA CHMP plenary meeting is scheduled for 9 March 2021. Through a Post-approval Change Management Protocol (PACMP) the applicant is considering scaling up current production capacities as well as the inclusion of other sites to expand the

⁶ WHO TRS 978 Annex 6

manufacturing of the drug substance and the drug product. This will include the filling site at Aspen SVP located in Port Elizabeth, South Africa (expected by April 2021).

The assessment of the Covid-19 Vaccine Janssen consisted of the evaluation of relevant quality data, with emphasis in the critical attributes and programmatic characteristics of the vaccine.

The information reviewed in this procedure included the following:

Drug Substance

- Manufacture, process controls and characterization
- Specifications and analytical methods
- Batch analysis
- Reference materials
- Container closure system
- Stability

Drug Product

- Description of the product and Pharmaceutical development
- Manufacture of the product and process controls
- Product specifications and analytical methods
- Batch analysis
- Reference materials
- Container closure system
- Stability and programmatic suitability
- Conditions to be used for international shipment
- Review of package inserts and labelling, as per WHO EUL requirements

3.2 Non-clinical overview

The nonclinical testing strategy covers the nonclinical pharmacology testing with the immunogenicity and efficacy data, and an assessment of the theoretical risk of vaccine-associated enhanced respiratory disease (VAERD) supplemented with the pharmacokinetic (biodistribution), and toxicology testing. An integrated assessment of the biodistribution profile of the Ad26 vector, as well as the nonclinical safety profile of Ad26.COVS, based on an Ad26.COVS-specific repeat-dose and local tolerance study, and a developmental and reproductive toxicity study are presented. To further support the toxicological evaluation of Ad26.COVS, toxicology data from other Ad26-based vaccines are provided.

Pharmacology

Immunogenicity data from studies in mice, rabbits, Syrian hamsters, and non-human primates (NHP) show that a single dose of Ad26.COVS induces humoral and cellular immune responses as early as 2 weeks post immunization. Ad26.COVS induces neutralizing antibodies and a Th1 skewed immune response, factors that are thought to be beneficial to minimize potential risk of VAERD.

To investigate whether there were any indications of VAERD, 2 challenge models (Syrian hamster (2 studies performed) and NHP) were considered with histopathologic analysis of lung tissues after

Ad26.COV2.S vaccination and subsequent respiratory inoculation with SARS-CoV-2. The studies showed no indications of VAERD based on monitoring of clinical signs and viral load of Ad26.COV2.S vaccinated animals after SARS-CoV-2 challenge, and based on histopathologic assessment of lung tissue from these animals compared with challenged control animals. In both Syrian hamsters and NHP, SARS-CoV-2 specific binding and neutralizing antibodies significantly correlate with protection from infection with SARS-CoV-2

Biodistribution

Biodistribution studies in rabbits showed a pattern of limited distribution of the Ad26vector. Clearance of the Ad26 vector was observed following IM injection, indicating that the vector does not replicate and/or persist in the tissues.

As biodistribution is considered dependent on the viral vector platform and not on the transgene insert, the biodistribution results obtained with Ad26.ENVA.01 and Ad26.RSV.preF are considered sufficient to inform on the biodistribution profile of Ad26.COV2.S when administered via the same (i.e., IM) route.

Toxicology

Ad26.COV2.S administered on three occasions over 4 weeks (i.e., every 2 weeks) at 1×10^{11} vp/dose in the toxicity studies was well tolerated and was not associated with any adverse vaccine-related effects. The vaccine dose level and dosing volume as well as the number of injections exceed the single-dose vaccine regimen at 5×10^{10} vp, as a 0.5-mL injection as proposed in humans. Hence the full human dose was covered.

The vaccine-related effects noted were considered to reflect a normal, immunologic response consistent with vaccination. The nonclinical safety profile of Ad26.COV2.S is largely similar to the profile observed previously for other Ad26-based vaccines. The combined reproductive and developmental toxicity study EF-PPND did not reveal any evidence of impaired female fertility and did not indicate harmful effects with respect to reproductive toxicity. In addition, the repeat-dose toxicity studies with Ad26.COV2.S or other Ad26-based vaccines have not revealed any effects on male sex organs that would impair male fertility.

In conclusion, nonclinical studies in mice, rabbits, Syrian hamsters and NHP established a safe dose and regimen with evidence of immunogenicity and efficacy. The nonclinical data did not show any adverse vaccine-related effects and support the use of Ad26.COV2.S in humans. Development and Reproductive toxicity studies indicated that the vaccine may be safe to use in pregnant women. This has to be confirmed by the activities included in pharmacovigilance plan.

3.3 Clinical overview

There are five ongoing clinical studies with Ad26.COV2.S summarized in the Table-1 below.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Janssen Ad26.COV2.S (COVID-19) Vaccine

Study Number	Phase /Type (Efficacy, Safety)	Participants Planned (N)	Test Product(s); Dosing Regimens	Study Status	Countries
3001	Phase 3 efficacy, safety	40,000 adults	Ad26.COV2.S 5x10 ¹⁰ vp 1-dose regimen	Enrollment complete	USA, Argentina, Brazil, Chile, Peru, Mexico, Colombia, South Africa
3009	Phase 3, efficacy, safety	30,000 adults	Ad26.COV2.S 5x10 ¹⁰ vp 2-dose regimen	Enrollment ongoing	Europe, South Africa, North America, Latin America, Asia
2001	Phase 2a safety, immunogenicity	550 adults 660 adolescents	Ad26.COV2.S 1x10 ¹¹ vp 5x10 ¹⁰ vp 2.5x10 ¹⁰ vp 1.25x10 ¹⁰ vp; 1- and 2-dose regimens	Enrollment of adults ongoing; enrollment of adolescents not started	The Netherlands, Germany, Spain
1002	Phase 1 safety, immunogenicity	250 adults	Ad26.COV2.S 5x10 ¹⁰ vp, 1x10 ¹¹ vp; 2-dose regimen	Enrollment complete	Japan
1001	Phase 1/2a safety, immunogenicity	1045 adults	Ad26.COV2.S 5x10 ¹⁰ vp & 1x10 ¹¹ vp; 1-dose and 2-dose regimens, with booster in 1 cohort	Enrollment complete	USA, Belgium

The design and results of the pivotal phase 3 trial are reviewed in line with the documents “Considerations for evaluation of Covid-19 vaccines: Points to consider for manufacturers of Covid-19 vaccines” Version 25, November 2020, and “WHO Target Product Profiles for Covid-19 Vaccines” Version 3-29 April 2020

3.3.1 Vaccine efficacy

A single IM dose of Ad26.COVS.2 at 5×10^{10} vp was selected as the final regimen for use in the pivotal Phase 3 study VAC31518COV3001 (COV3001) based on interim data from the Phase-I/II study, COV1001.

This study COV3001 is the cornerstone of this submission and the focus of the EUL review.

COV3001 is an ongoing randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of Ad26.COVS.2 administered as a single dose in adults ≥ 18 years of age conducted in North America, Latin America and South Africa. A target of 40,000 adults were to be randomized 1:1 to receive intramuscular injections of either vaccine (5×10^{10} vp) or placebo.

COV3001 initiated on 21 September 2020 in the USA was conducted during a period of very high SARS-CoV-2 transmission, including new variants, in a pandemic.

At the end of 2020, the emergence of new SARS-CoV-2 variants in some countries became apparent: in South Africa (20H/501Y.V2 belonging to the B.1.351 lineage), Brazil (20J/501Y.V3 and strains belonging to the P.2 lineage), the US (CAL.20C belonging to the B.1.429 lineage) and the UK (20I/501Y.V1 belonging to the B.1.1.7 lineage).

At the time of the primary analysis, 464 moderate to severe/critical COVID-19 cases, with onset at least 14 days after vaccination, were included in the Per Protocol analysis set, of which 259 cases occurred at least 28 days after vaccination. The total number of moderate to severe/critical COVID-19 cases allowed for robust analyses overall and in some individual countries (US, Brazil, South Africa) or regions (Latin America).

The **overall VE against moderate to severe/critical COVID-19** (95% CI) was 66.9% (59.03; 73.40) (116 versus 348 cases in the placebo group) and 66.1% (55.01; 74.80) (66 versus 193 cases in the placebo group) from at least 14 and at least 28 days after vaccination, respectively.

- The VE (95% CI) against moderate to severe/critical COVID-19 with onset at least 14 days and at least 28 days after vaccination was 76.3% (61.58; 86.04) (21 versus 88 cases in the placebo group) and 66.2% (36.74; 82.99) (14 versus 41 cases in the placebo group), respectively, **in adults ≥ 60 years of age**.
- The VE (95% CI) against moderate to severe/critical COVID-19 with onset at least 14 days and at least 28 days after vaccination 63.7% (53.87; 71.58) (95 versus 260 cases in the placebo group) and 66.1% (53.30; 75.77) (52 versus 152 cases in the placebo group), respectively, **in adults < 60 years of age**.
- The VE (95% CI) against moderate to severe/critical COVID-19 with onset at least 14 days and at least 28 days after vaccination 85.1% (61.46; 95.49) (5 versus 31 cases in the placebo group) and 77.0% (28.76; 94.41) (4 versus 16 cases in the placebo group). respectively, **in adults ≥ 70 to ≤ 79 years of age**.

The VE against **severe/critical COVID-19** (95% CI) was 76.7% (54.56; 89.09) (14 versus 60 cases in the placebo group) as of 14 days and 85.4% (54.15; 96.90) (5 versus 34 cases in the placebo group) as of 28 days after vaccination, consistent across age groups, countries, and regions.

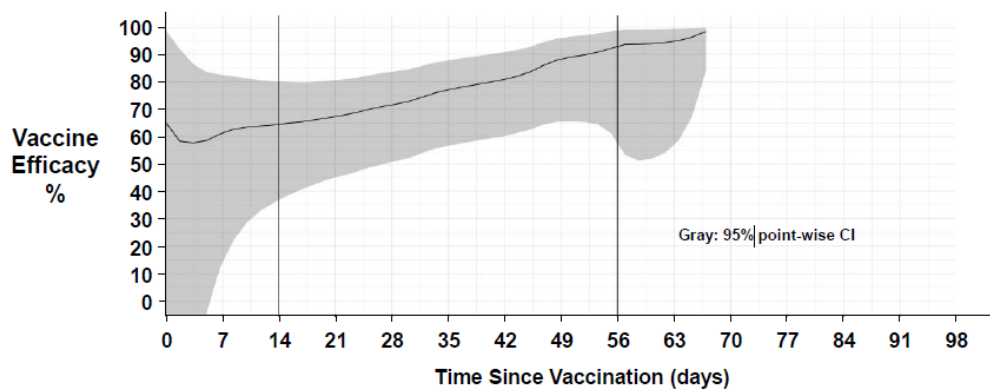
The VE against **COVID-19 related hospitalizations** (including ICU admission, mechanical ventilation and ECMO) (95% CI) was 93.1% (72.74; 99.20) (2 versus 29 cases in the placebo group) as of 14 days and 100% (74.26; 100.00) (0 versus 16 cases in the placebo group) as of 28 days after vaccination.

Impact of Ad26.COVS2 vaccination on COVID-19 associated deaths was also observed. In accordance with WHO COVID-19 case definition, all 3 deaths in Ad26.COVS2 group were classified as “Not COVID-19” and 8 out of 16 in the Placebo group. Thus 8 were COVID-19 associated deaths (2 Probable and 6 Confirmed) and all occurred in South Africa.

Onset of VE against severe/critical COVID-19 began as of 7 days after vaccination and against moderate to severe/critical COVID-19 as of 14 days after vaccination. **Vaccine efficacy increased through Day 56, especially for severe/critical COVID-19.**

Vaccine Efficacy Against Severe/Critical COVID-19 Increased Over Time Through Day 56

CO-41



Days of follow-up	7	14	28	42	56	70	84	98
% of participants with follow-up	~100%	~100%	99%	93%	55%	20%	4%	2%

COV3001; Full Analysis Set; baseline seronegative; confirmed: positive PCR centrally confirmed COVID-19 cases

The VE (95% CI) against COVID-19 per the US FDA harmonized definition was in line with the observed VE against any symptomatic COVID-19: 67.2% (59.32;73.67) and 66.7% (55.63; 75.23) at least 14 days and at least 28 days after vaccination, respectively.

SUBGROUP ANALYSES

To allow for the largest possible dataset, subgroup analyses described in the paragraph below are based on all COVID-19 cases with at least 1 positive PCR result from either the study sites or the central laboratory when the confirmation is available. The differences in VE between subgroups could be due to small numbers (low number of cases) and differences in the length of follow-up after vaccination. Further follow-up within the study and post marketing studies to obtain more cases in the various subgroups and reduce the effect of short follow up time on VE estimates will provide more detail and allow for a better understanding of some of the subgroup analyses.

- **On country level**, most of the participants were enrolled in the **US, Brazil, South Africa and Colombia**.

- In the US , the VE (95% CI) against all **moderate to severe/critical** COVID-19 was 74.4% (65.00; 81.57) and 72.0% (58.19; 81.71) as of day 14 and day 28, respectively.
- In South Africa this was 52.0% (30.26; 67.44) and 64.0% (41.19; 78.66), respectively.
- In Brazil this was 66.2% (51.01; 77.14) and 68.1% (48.81; 80.74), respectively.
- In the US , the VE (95% CI) against all **severe/critical** COVID-19 was 78.0% (33.13; 94.58) and 85.9% (-9.38; 99.69), as of day 14 and 28, respectively.
- In South Africa VE was 73.1% (40.03; 89.36) and 81.7% (46.18; 95.42), respectively.
- In Brazil VE was 81.9% (17.01; 98.05) and 87.6% (7.84; 99.72), respectively.

- **Variants:**

- In South Africa 94.5% had the 20H/501Y.V2 variant (B.1.351 lineage),
- in Brazil 69.4% had a variant from the P.2 lineage and 30.6% had the Wuhan-Hu1 reference sequence+D614G variant,
- in US 96.4% had the Wuhan-Hu1 reference sequence+D614G and 2.5% had the CAL.20C variant.

-The VE in participants **with co-morbidities** against **moderate to severe/critical COVID-19** (95% CI) was 64.2% (52.68; 73.14) (70 versus 194 cases in the placebo group) and 58.6% (40.57; 71.55) (44 versus 105 cases in the placebo group), at 14 and 28 days after vaccination. And those **without co-morbidities** was 67.6% (59.38; 74.30) (103 versus 315 cases in the placebo group) and 68.8% (58.98; 76.58) (69 versus 219 cases in the placebo group), at 14 and 28 days after vaccination. There were fewer participants with co-morbidities than without co-morbidities (N <7,800 vs >11,500), resulting in a lower number of person-years (approximately 1,100 vs approximately 2,000) for case accrual in the subgroup of participants with comorbidities

-The VE in participants with **co-morbidities** against **severe/critical COVID-19** (95% CI) was 75.6% (50.56; 89.12) (10 versus 41 cases in the placebo group) as of 14 days after vaccination and 75.2% (30.03; 92.74) (5 versus 20 cases in the placebo group) as of 28 days after vaccination.

The **combination of older age and comorbidity resulted in a difference in the point estimates of VE**. The point estimate for VE (95% CI) against moderate to severe/critical COVID-19 as of 28 days after vaccination in participants ≥ 60 years of age **without comorbidities** was 72.4% (45.04; 87.25) (11 versus 39 cases in the placebo group), while the point estimate for participants ≥ 60 years **with comorbidities** was 42.3% (-13.14; 71.57) (15 versus 26 cases in the placebo group).

This observed difference should be followed up closely as this may warrant a different vaccination approach for this older age group with comorbidity. The explanation of the observed differences in VE by the applicant is based on the relatively low number of cases and differences in length of follow-up (shorter) after vaccination (related to the design of the study). As indicated in the RMP, further follow-up within the study and post marketing studies to obtain more cases and reduce the effect of short follow up time on VE estimates will provide more detail and allow for a better understanding of the impact of comorbidity, age, or both on the vaccine effectiveness.

-Vaccine efficacy was consistent between Black/African Americans and Whites, between Hispanics and non-Hispanics and between sexes.

-VE appears to be lower in the American Indian/Alaskan population.

-At the regional level, the VE (moderate to severe) of Latin America is comparable to Southern Africa and slightly lower than Northern America.

The Asian population is largely under-represented on the entire development program. This should be addressed more specifically in PMS plan.

-There are **not enough data available** to draw conclusions regarding the **VE against Asymptomatic or Undetected SARS-CoV-2 infection**, or impact of vaccination on **viral load** in breakthrough cases.

Duration of protection.

As the analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

3.3.2 Vaccine safety

A robust clinical safety database is available consisting of all adult participants who received at least 1 dose of Ad26.COVS.2 in the Phase 3 studies COV3001 and COV3009, the Phase 2a study COV2001, the Phase 1 study COV1002, and the Phase 1/2a study COV1001.

- Up to the exposure cut-off date, the **safety database** includes a total of **54,586 adults ≥18 years** of age (of which 17,940 participants were ≥60 years, 10,746 were ≥65 years, and 1,848 were ≥75 years) who received Ad26.COVS.2 or placebo. Of these 54,586 adults, **1,596 adults received 2 doses of Ad26.COVS.2 or Placebo**.
- A total of **27,181** (of which 8,869 participants were ≥60, 5,257 were ≥65, and 952 were ≥75) received at least 1 dose of Ad26.COVS.2 at the selected dose level of 5x10¹⁰ vp.
- At the time of the primary analysis, the **median follow-up** after vaccination was **58 days** and 23,903 (54.6%) participants in the full analysis set (FAS) had at least 2 months (8 weeks) of follow-up.
- **Longer safety follow-up of >2 months** is available for **over 23,000** participants in the FAS (11,948 in the Ad26.COVS.2 group and 11,955 in the placebo group).
- In the FAS, 45.0% of participants were **female** and 54.9% were **male**. The median age was **52 years (range 18 to 100 years)**. The median **BMI was 27.00 kg/m²** (interquartile range: 23.90; 30.70 kg/m²). Age distribution was 33.5% of participants ≥60 years and 22.9% of participants ≥18 to <40 years. In total 19.6% and 3.5% of the participants were ≥65 and ≥75 years, respectively. **9.6%** of participants were **SARS-CoV-2 seropositive** at baseline equally distributed between the Ad26.COVS.2 and placebo group. A total of **40.8%** of participants had **1 or more comorbidities** at baseline associated with increased risk of progression to severe COVID-19. **Most common comorbidities were** obesity (28.5%), hypertension (10.3%), type 2 diabetes mellitus (7.3%), serious heart conditions (2.3%), and asthma (1.3%). Other comorbidities were present in ≤1% of the participants. A total of 1,218 (**2.8%**) **HIV-infected** participants were enrolled. Of the 7,616 women of childbearing potential enrolled, 285 (**3.7%**) were **breastfeeding**.

Pivotal Clinical Safety Experience (Study COV3001)

Solicited Local Adverse Events (7-day post-vaccination period)

The most frequently reported solicited local AE (>45% of participants in the Ad26.COV2.S group) was **vaccination site pain**. Both vaccination site erythema and swelling were reported in <8% of participants in the Ad26.COV2.S group.

Most solicited local AEs were **Grade 1 or Grade 2** in severity and the frequency of Grade 3 solicited local AEs was low overall. The most frequently reported **Grade 3** solicited local AE was **vaccination site pain reported in <0.5% of participants in the Ad26.COV2.S group**. No Grade 4 solicited local AEs were reported.

All solicited local AEs were transient in nature, resolving in 2 to 3 days.

Solicited Systemic Adverse Events (7-day post-vaccination period)

The most frequently reported solicited systemic AEs ($\geq 30\%$ of participants in the Ad26.COV2.S group) were **fatigue, headache, and myalgia**. Other solicited systemic AEs were reported in <15% of participants in the Ad26.COV2.S group.

Most solicited systemic AEs were **Grade 1 or Grade 2** in severity and the frequency of Grade 3 solicited systemic AEs was low overall. All **Grade 3** solicited systemic AEs were reported in **<2.0% of participants in the Ad26.COV2.S group**. No Grade 4 solicited systemic AEs were reported.

Pyrexia (fever defined as body temperature $\geq 38.0^\circ\text{C}$, as recorded by the participants) was reported in **9.0%** of participants in the Ad26.COV2.S group compared to 0.6% of participants in the placebo group. **Grade 3 pyrexia was reported in 0.2%** of participants in the Ad26.COV2.S group of which the majority occurred in the **younger age groups**. No Grade 3 pyrexia was reported in the placebo group. **All fevers were reported to have started on the day of vaccination (Day 1) or the day after (Day 2)** and had a median duration of **1 day** after vaccination with Ad26.COV2.S. Of the 302 participants who experienced fever in the Ad26.COV2.S group, 202 (66.9%) used **antipyretics**.

Most solicited systemic AEs were transient in nature, resolving in 1 to 2 days.

Unsolicited Adverse Events (28-day post-vaccination period)

Overall, for adults, there was **no apparent difference in unsolicited AEs reported** between groups. All unsolicited AEs had frequency **below 10%**.

The most frequently reported unsolicited AEs were **chills, nasal congestion, arthralgia, cough, and diarrhea**.

Most unsolicited AEs were **Grade 1 or Grade 2** in severity.

Unsolicited AEs of at least **Grade 3** were reported equally in both groups (**0.6%** Ad26.COV2.S group - placebo group) with 0.1% considered to be related to the study vaccine in the Ad26.COV2.S group.

Immediate Adverse Events (30 minutes after vaccination)

No anaphylactic or severe hypersensitivity reactions were observed within 30 minutes after vaccination. Solicited and unsolicited immediate AEs occurring within 30 minutes after vaccination were infrequent, similar in both groups (0.5% Ad26.COV2.S - 0.3% placebo) and none considered serious. These findings are consistent with the safety data of the Ad26-vector platform.

Deaths

Up to the cut-off date of 22 January 2021, **19 deaths** were reported, 3 in the Ad26.COVID-19 group and 16 in the placebo group, all of which were considered unrelated to the study vaccine by the investigator. In the **Ad26.COVID-19 group**, 3 deaths were reported due to lung abscess, [non-COVID-19] pneumonia, and 1 of unknown cause at the time of data cut-off.

In the **placebo** group, 16 deaths were reported and the causes of death by PT were suicide, acute myocardial infarction, accidental overdose (illicit drug overdose), malaise/diabetes, cardiac failure, suspected COVID-19, COVID-19 (5 deaths), [non-COVID-19] pneumonia (2 deaths), and 3 deaths of unknown cause.

In accordance with WHO COVID-19 case definition, the 3 deaths in Ad26.COVID-19 group were classified as “Not COVID-19” and 8 in the Placebo group (2 Probable COVID-19 and 6 Confirmed COVID-19).

Serious Adverse Events and (S)AEs leading to Study Discontinuation.

Up to the cut-off date of 22 January 2021, **0.4%** in the Ad26.COVID-19 group and **0.6%** in the placebo group reported 1 or more SAEs. 0.1% participants reported **a total of 10 SAEs which were considered to be related to the study vaccine** by the investigator but not always by the applicant.

- Of these 10 related **SAEs**, 7 were reported in **7 participants in the Ad26.COVID-19 group**: Grade 4 Guillain-Barré syndrome (16 d post vacc), Grade 4 pericarditis (17 d post vacc), Grade 3 brachial radiculitis (immediately post vacc), Grade 3 post-vaccination syndrome (2d post vacc), Grade 3 Type IV hypersensitivity (3 d post vacc), Grade 2 facial paralysis (Bell’s Palsy/ 3 d post vacc), Grade 2 facial paralysis (Bell’s Palsy 16 d post vacc).
- Of these 10 related SAEs, 3 were reported in **2 participants in the placebo group**: Grade 4 deep vein thrombosis (DVT) (6d post vacc), Grade 3 Epstein-Barr virus (EBV) infection (14d post vacc and a Grade 3 atrial flutter (21d post vacc).

One additional SAE of **transverse sinus thrombosis** resulting in cerebral hemorrhage was initially considered to be related to blinded study vaccine and led to a pause in study vaccination in all ongoing studies with Ad26.COVID-19. After review of additional information and follow-up assessments by the investigator, **the causality was reassessed as not related to the study vaccine** by the investigator and the Applicant (received Ad26.COVID-19 after unblinding).

Up to the cut-off date of 22 January 2021, 0.4% participants reported at least 1 non-COVID-19 SAE in the Ad26.COVID-19 group compared to 0.4% participants in the placebo group, showing **no imbalance of non-COVID-19 SAEs between both groups by SOC** (System Organ Classes).

Medically-attended Adverse Events (MAAE) (up to 6 M post vaccination)

Up to the cut-off date of 22 January 2021, 1.4% participants reported 1 or more MAAEs in the Ad26.COVID-19 group compared to 1.9% participants in the placebo group. The **most frequently** reported MAAE ($\geq 0.5\%$ of participants in any vaccine group) were **infections and manifestations by SOC**. By PT, **COVID-19 infection was the most frequently reported** MAAE 0.1% of participants in the Ad26.COVID-19 group compared to 0.2% participants in the placebo group.

Adverse Events of Interest

As per protocol, **there were no pre-specified adverse events of special interest for Ad26.COVS.2 clinical development.** A list of selected AEs of interest were reviewed in the database and showed a numerical imbalance between the 2 groups.

Up to the cut-off date of 22 January 2021, **no severe allergic reactions (including anaphylaxis) have been reported in the studies** and have not been identified as a safety issue in the data available for Ad26- based vaccines.

Other Adverse Events of Interest showing a numerical imbalance were **tinnitus, convulsions/seizures, thrombotic and thromboembolic events, demyelinating disorders.** Besides the numerical imbalances with low number of cases, there were **no notable patterns or numerical imbalances between the Ad26.COVS.2 and placebo group for specific categories of (S)AEs** (including neurologic, neuroinflammatory, and cardiovascular events) that would suggest a causal relationship to the Ad26.COVS.2 vaccine. The absence of a causal link is further enforced by the safety data from the Ad26- platform.

Pregnancies

Up to the cut-off date of 31 December 2020, 8 pregnancies were reported in the GMS database for the COV3001 study.

In addition, the Ad26-based vaccine database (>193,000 participants), did not reveal any safety concerns in general nor did it reveal any safety concerns related to exposure to Ad26-based vaccines during pregnancy.

Vital Signs

Up to the cut-off date of 22 January 2021, no Grade 3 vital sign-related AEs were observed after vaccination with Ad26.COVS.2 in study COV3001. Two Grade 3 hypertension AEs were reported after vaccination with placebo which were considered unrelated to the study vaccine.

CONCLUSION

Overall, all safety data (including reactogenicity) from the Phase 3 study COV3001 from 43,783 participants (including 6,736 participants in the safety subset) who received either vaccine or placebo with a median of 2 months of follow-up after vaccination show that a single dose of Ad26.COVS.2 at a dose level of 5×10^{10} vp has an acceptable safety and reactogenicity profile in participants ≥ 18 years of age. **Lower reactogenicity was observed for older adults** (≥ 60 years of age) compared to younger adults (≥ 18 to < 60 years of age) among participants vaccinated with Ad26.COVS.2. Reactogenicity to Ad26.COVS.2 in adults ≥ 18 years of age was demonstrated to be transient and most solicited AEs generally resolved in 1 to 2 days post vaccination.

Overall, no clinically relevant differences in the reactogenicity profile of Ad26.COVS.2 were observed **across sex, race/ethnicities, geographies, comorbidities, SARS-CoV-2 or HIV serostatus at baseline. No overall differences in safety** were observed between **older adults** (≥ 60 years and ≥ 75 years of age and **younger adults** (≥ 18 to < 60 years of age).

In general, the safety profile observed in the Phase 3 study COV3001 is consistent with the safety profile observed in the Phase 1 and 2 studies (COV1001, COV1002, and COV2001) except for fever.

By region, the frequencies of pyrexia were 3.6% (no Grade 3) in South Africa, 13.4% (0.4% Grade 3) in Latin America and 6.8% (0.2% Grade 3) in US in COV3001 versus 6.2% (1.2% Grade 3) in US and 14.5% (3.9% Grade 3) in Belgium in COV1001.

Clinical Safety Experience with the other studies

Adverse Events of Ad26.COV2.S by Dose Level.

No safety issues were identified after vaccination with **higher doses up to 1×10^{11} vp**.

Adverse Events of Ad26.COV2.S Administered as a 2-Dose Regimen

In general, there was **no apparent difference** in the overall frequencies of solicited local AEs, solicited systemic AEs, and unsolicited AEs after vaccination with 5×10^{10} vp Ad26.COV2.S post-dose 1 compared to post-dose 2 in adults ≥ 18 to ≤ 55 years of age and adults ≥ 65 years of age. **All solicited local AEs and the majority of solicited systemic AEs were Grade 1 or 2 in severity.** Lower frequencies of Grade 3 solicited systemic AEs were observed after a second vaccination with Ad26.COV2.S in both age groups.

As expected, higher frequencies of pyrexia were observed after vaccination with Ad26.COV2.S **post dose 1 compared to post dose 2 in both age groups.**

In conclusion, no safety issues were identified after vaccination with 2 doses of 5×10^{10} vp Ad26.COV2.S.

Deaths, Other Serious Adverse Events, and AEs Leading to Study/Vaccine Discontinuation from Supportive Clinical Studies (COV1001, COV1002, COV2001, COV3009)

Up to the cut-off date of 11 January 2021, 1 death (accidental death) was reported and few SAEs were observed. Early discontinuations of vaccination or study due to (S)AEs were infrequent in all groups.

Across studies COV1001, COV1002, COV2001, and COV3009, a total of **26 participants reported 1 or more SAEs**. Of these 26 participants, 2 participants reported a total of 2 SAEs (COV1001) which were considered to be **related to the study vaccine**:

- **Grade 3 pyrexia** reported approximately 6 hours post dose 1 (received active vaccine at the 1×10^{11} vp dose level) and resolved the next day. **Considered related to the study vaccine by the investigator which led to discontinuation** of further vaccination.
- **Grade 2 multiple sclerosis** reported during post-dose 1 follow-up (received placebo); this **led to discontinuation** of further vaccination. The SAE was **considered related to the study vaccine by the investigator**. Based on the imaging findings, the event was **assessed by an expert neurologist as likely chronic in origin and preceding vaccination and therefore considered unrelated by the Applicant**.

In addition, **7 unrelated SAEs** (Grade 4: nephrolithiasis, lung adenocarcinoma, COVID-19-associated pleuritic pain and delirium [both in the same participant], 2 cases of COVID-19; Grade 3: COVID-19-associated cough) and 18 nonserious AEs (8 Grade 1 COVID-19 infections, 3 Grade 4 pyrexia, 2 Grade 3 blood pressure increased, 2 Grade 4 COVID-19 infections, 1 Grade 3 cough, 1 Grade 1 paraesthesia and 1 Grade 2 atrial flutter) led to discontinuation of the vaccine or study.

Medication Error/Immunization Error

To date, medication errors occurred **infrequently** during the conduct of studies COV1001, COV2001, and COV3001 without any safety issues. The **majority of medication errors** included participants receiving **the wrong vaccine**, such as participants received placebo instead of Ad26.COV2.S and vice versa.

In the Phase 1 and 2 studies with Ad26.COV2.S, **no safety issues** were identified after vaccination **with higher doses** up to 1×10^{11} vp using vials with an extractable volume of more than 1 mL. **Although more reactogenicity was observed** after vaccination with Ad26.COV2.S at a dose level of **1×10^{11} vp**, **the safety profile of this dose was considered to be acceptable.**

Therefore, accidental administration of higher doses using multi-dose vials should not pose any known risk if the administered dose is not exceeding 1×10^{11} vp Ad26.COV2.S. In addition, **no safety issues were identified after vaccination with 2 doses of 5×10^{10} vp Ad26.COV2.S.** Therefore, accidental administration of a second dose of 5×10^{10} vp Ad26.COV2.S would not pose any known risk.

Supporting Clinical Safety Experience with Ad26-based Vaccines (Ebola, HIV, RSV studies)

As of 21 December 2020, Ad26-based vaccines have been administered to **>193,000** participants. The review of all available safety data with Janssen's Ad26-based vaccines to date concluded that, overall, these vaccines were **well tolerated, at all dose levels** studied (**range 1×10^9 vp to 1.6×10^{11} vp**) and **irrespective of the populations** studied (including younger adults, children and adolescents, elderly, HIV-infected participants, and participants with pre-existing Ad26 neutralizing antibody titers) and the **antigen transgenes** that have been used in the different programs. No significant safety issues have been identified to date.

Theoretical Risk of VAED, VAERD

The **potential risk** for predisposition of VAED, with a focus on VAERD, through vaccination with Ad26.COV2.S has been **evaluated in nonclinical challenge models** (non-human primates and Syrian hamsters) and **complemented with precautionary measures in the phase 3** study at the clinical level **and at the statistical design and monitoring level.**

- 3 challenge studies with NHP and Syrian hamsters. Monitoring of clinical signs and of respiratory viral load and lung histopathology assessment was performed in Ad26.COV2.S immunized Syrian hamsters and NHP after SARS CoV-2 challenge, and in comparison with unvaccinated and SARS-CoV-2 infected control animals. In addition, immunogenicity was assessed to show induction of neutralizing antibodies and a Th1 skewed immune response.
- The interim immunogenicity analysis of study COV1001 (see Section 4.1.3) clearly indicates that Ad26.COV2.S is able to elicit a cellular response with Th1-skewed CD4 response as well as to induce a high level of neutralizing antibodies.
- In study COV3001, continuous monitoring for VAED/VAERD was performed through the external Statistical Support Group who looked at each of the diagnosed Full Analysis Set COVID-19 events.

3.3.3 Immunogenicity

Humoral responses

No formal statistical testing of the immunogenicity data from the ongoing studies has been conducted. Descriptive statistics (geometric mean and CI, or median and interquartile range Q1-Q3, as appropriate)

were calculated for continuous immunologic parameters at all timepoints. Geometric mean fold rises from baseline and corresponding 95% CI were additionally calculated.

In the placebo groups, no humoral response was observed at any of the time points (day 14 and day 28).

Overall, no difference was observed in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S between Brazilian, South African and US participants. S-specific binding antibody concentrations for participants at Brazilian, South African and US sites increased from baseline (GMC < LLOQ) to Day 29 with GMCs of 402 (95% CI: 302; 505), 388 (95% CI: 297; 506) and 412 (95% CI: 306; 554), respectively, representing geometric mean increases from baseline of more than 6-fold to 9.3-fold. The responder rates were similar across sites from all 3 countries with >93% for the active vaccine groups. Similar GMCs and responder rates were observed across countries compared with overall COV1001 data

Impact of prior exposure to wild-type Ad26.

Baseline seropositivity to Ad26 was evaluated by Ad26 VNA in a population of 3,851 participants from three large Janssen's clinical studies (Ebola, HIV and RSV programs) across four continents and a wide range of age groups.

Ad26 seroprevalence varied by continent, with

- High seroprevalence reported in Africa (10 countries⁷) (77.9% [95% CI 75.9;79.7]), followed by Asia (41.4% [28.9;55], exclusively in Thailand)
- Comparatively low seroprevalence levels in North America (15.1% [13.5;16.9], exclusively USA), and Europe (11.6% [7.4;17.5]).

Within those individuals that were seropositive for Ad26 neutralization, GMTs and medians did not vary by continent or country. The overall GMT in the Ad26 seropositive participants across all continents was 163.9 (95% CI 153.7;174.8) and titers in Africa (GMT165.2 [154.1;177.1], N=1872), Asia/ Thailand (GMT 263.3 [136.4;508.3], N=58), Europe (GMT 147.4 [74.8;290.3], N=173), and North America/ USA (GMT 151.6 [126.2;182], N=1748) did not notably vary from that average, irrespective of regional differences in seroprevalence.

Similarly, no notable differences in GMTs were observed between the individual African countries.

In addition, only a very low number of participants in the **Phase 1 and 2 studies** had detectable pre-existing levels of **Ad26-neutralizing antibodies**.

In study COV3001, a subset of participants from Brazilian and US sites was selected to assess levels of pre-existing (baseline) Ad26 neutralizing antibodies.

-Participants from the US sites had no detectable Ad26 IC90 titers at baseline, with only 2% in the active vaccine group and 4.2% in the placebo group being seropositive.

-Participants from Brazil had an overall Ad26 seroprevalence of 32.5% and 28.4% in the active vaccine group and placebo group, respectively.

- Among the 27 Brazilian participants **with detectable Ad26 neutralizing antibodies** at baseline, 23 (**85.2%** [95% CI: 66.3; 95.8]) were **vaccine responders** as measured by S-ELISA at Day 29.

⁷ Burkina Faso, Cote d'Ivoire, Kenya, Mozambique, Nigeria, Rwanda Sierra Leone, Tanzania, Uganda and South Africa

- Among the 59 Brazilian participants with **no detectable Ad26 neutralizing antibodies** at baseline, 59 (**100%** [95% CI: 93.9; 100]) were **vaccine responders** as measured by S-ELISA at Day 29.
- A low negative correlation (Spearman correlation -0.378) was observed between **S binding antibody** levels at Day 29 post vaccination and **pre-existing Ad26** neutralizing antibodies at baseline.

Overall, similar S binding antibody levels and responder rates were observed across different sites, countries and regions irrespective of differences in pre-existing Ad26 neutralizing antibodies at the time of vaccination.

Janssen performed a pooled analysis of 11 clinical studies from two different vaccine programs (Ebola program: 8 studies and HIV program: 3 studies) which contain the same Ad26 platform. The purpose was to study the “Influence of Natural Pre-existing Immunity to Ad26 on Humoral Immune Responses post 1Ad26-based Vaccination”.

The available dataset was neither designed to be balanced across continents and countries nor did it exclude the impact of other cofactors, such as age, BMI (Body Mass Index), and sex. Irrespective of these caveats, no consistent pattern of apparent impact of baseline Ad26 neutralizing antibodies on the vaccine immune responses post dose 1 Ad26-based vaccination could be discerned within the available dataset. **The potential biological relevance of Ad26 seropositivity, in terms of impact on vaccine efficacy, is unclear and remains to be determined.** Cofactors, such as pre-existing Ad26 NABs, that can impact immunogenicity and efficacy of vaccine response, will continue to be monitored within Ad26-based vaccine programs.

Cellular responses

A single dose of Ad26.COVS.2 elicited SARS-CoV-2 CD4 and CD8 T-cell responses by Day 15 (14 days post dose 1) and up to Day 29 (28 days post dose 1) in adult participants ≥ 18 to ≤ 55 years and ≥ 65 years of age. In all participants with a CD4 T-cell response, the response was skewed towards the Th1 phenotype.

3.3.4 Special populations

Based on the data available to date, **no VE could be calculated in HIV-infected participants** (5 moderate to severe/critical cases with onset at least 14 days after vaccination in both the Ad26.COVS.2 and placebo group and 2 vs 4 cases with onset at least 28 days after vaccination, respectively). However, the low number of HIV-infected participants (< 500 per vaccination group resulted in a low number of person-years (approximately 70 per vaccination group) for case accrual and available data do not suggest a negative impact of the vaccine. **A prospective study in HIV is proposed in PMS plan.**

Persons with severe immunodeficiency, severe underlying disease, and pregnant/lactating women were excluded from the studies, therefore efficacy, immunogenicity and safety of Janssen Covid19 vaccine in these groups is currently unknown. Although data from Brazil, South Africa or Latin America have been submitted by the applicant, not all available data may be generalizable to populations in low and middle-income countries (LMIC) who have profiles that can impact on the efficacy of this vaccine (for example, ethnicity, concomitant infections and malnutrition).

3.4 Risk Management Plan

3.4.1 Product description

Acceptable.

3.4.2 Nonclinical information

Acceptable.

3.4.3 Clinical information

a. Important identified risks:

JC	WHO	Comments
Anaphylaxis	Anaphylaxis	Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. A minimum period of 15-minutes of observation is recommended for each vaccinee after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.

b. Important potential risks:

JC	WHO	Comments
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Although available data have not identified VAED as a concern for Ad26.COVS.S, the risk of VAED cannot be ruled out. VAED may be potentially serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention.
Venous thromboembolism	Venous thromboembolism	Due to the observed numerical imbalance and its potential life-threatening nature, the risk of VTE resulting from vaccination with Ad26.COVS.S, especially in participants with comorbidities associated with DVT and PE, cannot be entirely ruled out. Therefore, venous thromboembolism is considered an important potential risk.

	Programmatic errors	It may be necessary to minimize this situation in advance under real use conditions. It will be monitored via routine pharmacovigilance activities and will be presented in each PBRER/PSUR
--	---------------------	---

c. Missing information:

JC	WHO	Comments
Use during pregnancy	Use during pregnancy and while breastfeeding	Pregnant women not included in the clinical trials. Breastfeeding women were not excluded from the Phase 3 trials COV3001 and COV3009. To date, 128 breastfeeding women have received Ad26.COV2.S in trial COV3001, but no data to assess the safety profile are currently available in this subpopulation and the risk in this population has not yet been defined
Use in breastfeeding women		
Use in immunocompromised patients	Use in immunocompromised patients, including people living with HIV	The data in this population is limited (ongoing study) and it is possible that immune response to the vaccine may be different and compromise the effectiveness.
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	Frail individuals have not been included in the clinical studies, but old frail individuals have been prioritized for vaccination in practice.
Interaction with other vaccines	Interaction with other vaccines	The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g., influenza) has not been evaluated.
	Interchangeability or sequential use with other vaccines	The evidence to support interchangeability or sequential use of Ad26.COV2.S with other COVID-19 vaccines is still not available.
	Use in pediatric population <18 years of age	No efficacy data are available from participants ages <18 years.
Use in patients with autoimmune or inflammatory disorders	Use in patients with autoimmune or inflammatory disorders	There is limited information on the safety of Ad26.COV2.S in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.
Long-term safety	Long-term safety	Long-term safety profile of Ad26.COV2.S is currently limited and it is recognized that further follow-up for

		all vaccines is required. Additional activities will be needed to obtain such information.
	Impact of the emergence of variants on vaccine efficacy/effectiveness and safety	JC should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases as soon as available, irrespective of source.

3.4.4 Pharmacovigilance Plan

Routine pharmacovigilance activities: Acceptable in general, adverse reaction reporting, and signal detection are in accordance with national and international Good Pharmacovigilance (GPV) guidelines. The spontaneous reporting needs preferably be harmonized in most of the countries and with the sharing system with the VigiBase platform.

The monitoring of adverse events (AEs) of interest should consider anxiety-related reactions, tinnitus, convulsions/seizures, thrombotic and thromboembolic events (deep vein thrombosis, pulmonary embolism and venous thrombosis limb), demyelinating and neurological disorders, reactogenicity following vaccination and all serious adverse events, as included in routine pharmacovigilance in the submitted RMP.

Signal detection is proposed, an assessment of all AEs reported in Janssen’s safety database for Ad26.CO2.S will be performed monthly, and data mining review will be performed every three months. PSURs will be submitted every 6 months. The monthly safety reports will be prepared and submitted only for EMA and the applicant does intend submitting monthly summary safety reports to WHO if the WHO’s advisory group requires. For traceability, the applicant describes shipping conditions including automated temperature and location logging; labelling and barcoding; and vaccination cards / stickers. The applicant agreed to implement appropriate methods to ensure adequate traceability, that each batch delivered through COVAX can always be traced to COVAX.

Janssen is considering that for COVAX routine and additional pharmacovigilance activities as well as routine risk minimization activities will be managed through the EU RMP since it is not yet known to which countries the vaccine will be supplied to as part of COVAX. Nonetheless, there is a general concern about the collection of AEs in low- and middle-income countries (LMICs) of certain regions, because of the need for adequate pharmacovigilance systems. Therefore, Janssen is requested to ensure to that they receive data from all routine pharmacovigilance activities in all WHO regions.

Janssen is considering non-interventional and interventional studies as additional pharmacovigilance activities. The additional pharmacovigilance activities described in the EU RMP are intended for implementation in the European Economic Area (EEA) and US only. No additional pharmacovigilance activities are planned for other WHO regions. However, it is important to obtain additional information related to preventing laboratory confirmed SARS-CoV-2 hospitalizations and preventing medically attended COVID-19 up to 2 years post-vaccination in LMICs.

The applicant proposes the following studies in post authorization development plan:

1. Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients. To assess the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients (planned report date December 2023).
2. Post-authorization pregnancy exposure registry. At least one country of each WHO region would preferably be included.
3. Post-marketing safety study in Europe and USA. To assess the occurrence of pre-specified adverse events of special interest (AESIs) within specific risk periods following administration of Ad26.COV2.S.
4. Post-marketing Effectiveness Study in Europe and USA.
5. Safety and immunogenicity when co-administered with seasonal influenza vaccine will be studied. Details of the study design not yet available.

3.4.5 Risk minimization activities

The routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product. The applicant will host a Janssen COVID-19 vaccine-specific contact centre to support vaccination providers and recipients, based on that the applicant should also consider developing educational materials aimed at minimising the risk of immunisation errors (for example printed posters / guides), particularly for regions outside of Europe where providers may not readily have access to the contact centre. The applicant should implement these in all WHO regions and ensure the feasibility to measure these in all countries.

4 Outcome of review

4.1 Quality

The drug substance (DS) (Ad26.COV2.S) and the drug product (DP) (Covid-19 Vaccine Janssen) manufacturing processes and process controls are described in detail. Quality of process intermediates is adequately controlled by in-process controls. Both a small-scale process and a large-scale process are included in the EUL application. Manufacturing sites have valid Good Manufacturing Practices (GMP) certificates.

Critical quality attributes and critical process parameters were identified based on extensive AdVac/PER.C6 platform experience that was gained with other Ad26 viral vector-based products. The history of process development is summarized. In addition, process-related impurities have been characterized during clinical development of the current product and also during previous studies performed for other Ad26 viral vectors produced using the same platform technology.

Some process changes were introduced during clinical development and were qualified by a comparability analysis confirming the absence of any impact on product quality. Some further optimizations were introduced for the drug substance and drug product that will be used for the initial commercial batches. The applicant demonstrated comparability by a combination of release testing and

additional characterization testing. Results were similar. Therefore, it can be concluded that the materials from the commercial process at Janssen Vaccines (Leiden) are comparable to the lots used in the Phase 3 clinical trials.

The specifications proposed for the DS and DP are consistent and deemed acceptable.

Analytical methods for release and stability testing were described in detail. Non-compendial methods were properly validated. Compendial methods though not need to be validated were adequately verified by the company.

Container closure systems of DS and DP were properly qualified.

The proposed shelf life for the DS is 24 months when stored between -85°C and -40°C. The proposed shelf life for the DP is 24 months when stored frozen at -25°C to -15°C, and within these 24 months, 3 months when stored at 2 to 8°C. To highlight that these shelf lives are based on cumulative platform data from similar Ad26 products. The currently proposed shelf lives are deemed sufficiently qualified and justified and are thus acceptable.

Despite the highlight the level of completeness of the documentation submitted to WHO, there is some information that should be submitted to WHO as post-listing commitments, as referred below:

1. Product-specific stability data will be generated and will be provided when available. The proposed stability testing protocols are acceptable.
2. For thermal qualification for international shipments (air shipments), the company will be using the Va-Q-tainer USx M21G Pallet Container which has shown a satisfactory thermal performance, as per the information provided. However, in this regard the only remaining information needed is the specification of the monitoring device that will be use for the shipments. This information can be provided post EUL.
3. Actions derived from proposed PACMP.

4.2 Clinical

This clinical assessment raised limited number of queries and comments from the reviewers on clinical submitted evidence, as well as on issues related to the RMP. These have either been considered covered by the Janssen answers to the EMA CHMP list of questions or have been incorporated into the recommendations listed below and in the conclusion section of this document.

From the clinical point of review the Product Evaluation Group (PEG) recommended that an EUL may be granted by WHO to COVID-19 Vaccine Janssen provided that Janssen commits to meet the following conditions post-EUL:

1. The applicant should submit to WHO further interim analyses and the final clinical study reports of the ongoing studies (COV3001, COV3009, COV2001, COV1002 and COV1001) once they are completed.

2. Once available any relevant data coming from post EUL effectiveness studies should be shared with WHO, as this might change the benefit/risk profile of the vaccine in this population.
3. The applicant is urged to encourage participants, especially those not prioritized for vaccine access and not eligible for vaccines, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine
4. The RMP should also include/address the following:
 - Safety specifications:
 - Potential risks: add *programmatic error*
 - Missing information: add *use in paediatric population <18 years of age, and impact of the emergence of variants on vaccine efficacy/effectiveness and safety.*
 - *Interaction with other vaccines and interchangeability* should be considered separately from each other.
 - Pharmacovigilance plan
 - *The applicant is requested to submit the monthly reports mentioned in the RMP and the PSUR every 6 months. Janssen is requested to ensure that they receive available data from all routine pharmacovigilance activities in all WHO regions.*
 - *The applicant is requested to conduct non-interventional study(ies) for effectiveness, as part of the additional pharmacovigilance activities, in other WHO regions (LMICs). The effectiveness study(ies) should be conducted in LMICs, in particular in Asia and in African countries where no clinical studies were conducted. This request is additional to the 11 studies proposed by the applicant.*
 - *A summary of the protocol should be part of an updated version of the RMP.*
 - Risk minimization activities
 - *A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.*

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of Ad26.COVS. and to discuss with WHO in case of plans to make changes to the vaccine to address this issue. Janssen will monitor vaccine effectiveness linked to emerging variants based on long-term follow up on clinical trials 3001/3009 and by collecting sequence data in primary data collection observational study in Europe. In addition, Janssen is monitoring emerging mutations in public data bases and is supportive of establishment of international efforts for monitoring of emerging variants.

5 Technical considerations

5.1 Vaccine characteristics

One dose (0.5 ml) contains:

No less than 8.92 log₁₀ infectious units (IU) of the adenovirus type 26 (Ad26) vectored COVID-19 vaccine encoding the SARS-CoV-2 spike (S) protein⁸ (replication-incompetent, recombinant).

Qualitative composition of the Covid-19 Vaccine Janssen: 2-hydroxypropyl-Beta-cyclodextrin (stabilizer); citric acid monohydrate (buffer); ethanol (stabilizer); hydrochloric acid (pH adjuster); polysorbate-80 (stabilizer); sodium chloride (tonicity and stabilizer agent); sodium hydroxide (pH adjuster); trisodium citrate dihydrate (buffer) and water for injection (diluent).

There is no material of animal and/or human origin used in the formulation of this medicinal product. All of the excipients present in the formulation are of compendial grade.

The vaccine is a suspension for injection, colorless to slightly yellow, clear to very opalescent suspension. Vaccine vials should be inspected visually for particulate matter prior to administration.

The product contains no preservatives.

No diluent is required.

COVID-19 Vaccine Janssen is administered as a single dose of 0.5 mL from the multi-dose vial by intramuscular (IM) injection only, preferably in the deltoid muscle.

List of presentations available to UN Agencies/COVAX Facilities – multidose vials*

Presentation	Pharmaceutical form	Dose	Container	Pack Size
2.5 mL	Suspension for injection	0.5 mL	<p>Vial: 2R clear glass vial (Type 1)</p> <p>Stopper: Latex-free rubber stopper (chlorobutyl with fluoropolymer coated surface).</p> <p>Seal: Aluminium crimp and a blue plastic flip-off.</p>	Carton box containing 10 multidose vials.

*fill overage is not intended to increase the number of doses to be extracted from the vial.

5.2 Special precautions for storage and handling proposed by the applicant

Unopen Vaccine Vials

Unopen vaccine vials can be stored and/or transported frozen at -25°C to -15°C for up to 24 months and within these 24 months, 3 months when stored at 2 to 8°C.

⁸ Produced in the PER.CG[®] TetR Cell Line and by recombinant DNA technology

When stored frozen at -25°C to -15°C, a carton box of 10 vials or individual vials should be thawed overnight at 2°C to 8°C. At room temperature (maximally 25°C), a carton box of 10 vials will take approximately 2 hours to thaw, and individual vials will take approximately 1 hour to thaw.

The vaccine must not be refreeze once thawed.

The vaccine can also be stored in a refrigerator at 3 months when stored at 2 to 8°C for a single period of up to 3 months, not exceeding the original expiry date (EXP). Upon moving the product to 3 months when stored at 2°C to 8°C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should then be crossed out, denoting that is not the valid date under the above-described storage conditions.

The vial must be kept in the original carton in order to protect from light and to record the expiry for the different storage conditions, if applicable.

Before administering a dose of vaccine, health care giver should carefully mix the contents of the multi-dose vial by swirling gently (without shaking) in an upright position for 10 seconds.

Storage After First Opening (puncture) of the Vaccine Vial

The vaccine contains no preservatives.

In-use stability of the vaccine has been demonstrated for 6 hours at 2°C to 8°C. The product should preferably be used immediately after first puncture of the vial; however, it can be stored between 2°C to 8°C for a maximum of 6 hours otherwise discarded at the end of the immunization session, which ever come first, in compliance with the WHO Multidose Vial Policy.

5.3 Indication, warnings and contraindications

Therapeutic indications

COVID-19 Vaccine Janssen is indicated for active immunization for the prevention of coronavirus disease-2019 (COVID-19) in adults greater than or equal to 18 years of age.

The use of the vaccine should be in accordance with official recommendations.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1) [WHO Product Information].

Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reactions following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur with administration of injectable vaccines, including the COVID-19 Vaccine Janssen. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

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.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine Janssen may be lower in immunosuppressed individuals.

Limitations of vaccine effectiveness

Protection starts around 14 days after vaccination. As with all vaccines, vaccination with COVID-19 Vaccine Janssen may not protect all vaccine recipients (see section 5.1 of the WHO Product Information).

Excipients

Sodium

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

Ethanol

This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 mL dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

5.4 Posology and method of administration

Posology

Individuals 18 years of age and older

COVID-19 Vaccine Janssen is administered as a single dose of 0.5 mL by intramuscular injection only.

Paediatric population (<18 years of age)

The safety and efficacy of COVID-19 Vaccine Janssen in children and adolescents (less than 18 years of age) have not yet been established. No data are available.

Elderly (65 years of age and older)

No dose adjustment is required in elderly individuals ≥ 65 years of age. See also sections 4.8 and 5.1 of the WHO product information.

Method of administration

COVID-19 Vaccine Janssen is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

Before administering a dose of vaccine, carefully mix the contents of the multi-dose vial by swirling gently in an upright position for 10 seconds. Do not shake. Use a sterile needle and sterile syringe to extract a single dose of 0.5 mL from the multi-dose vial and administer by intramuscular injection only.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

Do not inject this product intravenously, subcutaneously, or intradermally.

There are no data available on the interchangeability of COVID-19 Vaccine Janssen with other COVID-19 vaccines. Do not use COVID-19 Vaccine Janssen as part of any other COVID-19 vaccine regimen.

5.5 Fertility, pregnancy and lactation

Pregnancy

There is very limited experience with the use of COVID-19 Vaccine Janssen in pregnant women. Animal studies with COVID-19 Vaccine Janssen do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development (see section 5.3) [of the WHO product information].

Administration of COVID-19 Vaccine Janssen in pregnancy may be considered when the potential benefits outweigh any potential risks to the mother and foetus.

Breast-feeding

It is unknown whether COVID-19 Vaccine Janssen is excreted in human milk.

Administration of COVID-19 Vaccine Janssen while breast-feeding should be considered when the potential benefits outweigh any potential risks to the mother and child.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

5.6 Interaction with other medicinal products and other forms of interaction

Concomitant use with other vaccines

No interaction studies have been performed. Concomitant administration of COVID-19 Vaccine Janssen with other vaccines has not been studied.

5.7 Safety profile

Summary of the safety profile

The safety of COVID-19 Vaccine Janssen has been assessed in an ongoing Phase 3 study (COV3001). A total of 21 895 adults aged 18 years and older received COVID-19 Vaccine Janssen. The study is being conducted in the USA, South Africa, Brazil, Chile, Argentina, Colombia, Peru and Mexico. In this study, 45.0% were female, 54.9% were male, 58.7% were White, 19.4% were Black or African American, 45.3% were Hispanic or Latino, 3.3% were Asian, 9.5% were American Indian/Alaska Native, 0.2% were Native Hawaiian or other Pacific Islander and 8.9% were of other racial/ethnic groups. The median age of individuals was 52.0 years (range 18-100). Individuals who were seropositive at baseline were included in the study (N=4 217). The safety analysis was performed once the median follow-up duration of 2 months after vaccination was reached.

In Study COV3001, the most common local adverse reactions ($\geq 10\%$) reported was injection site pain (48.6%). The most common systemic adverse reactions ($\geq 10\%$) were headache (38.9%), fatigue (38.2%), myalgia (33.2%) and nausea (14.2%). Pyrexia (defined as body temperature $\geq 38.0^\circ\text{C}$) was observed in 9% of participants. Most adverse reactions occurred within 1-2 days following vaccination and were mild to moderate in severity and of short duration (1-2 days).

Reactogenicity was generally milder and reported less frequently in older adults (763 adults ≥ 65 years old).

The safety profile was generally consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; a total of 2 151 adults seropositive at baseline received COVID-19 Vaccine Janssen (9.8%).

Tabulated list of adverse reactions

Adverse reactions observed during Study COV3001 are organised by MedDRA System Organ Class (SOC). Frequency categories are defined as follows:

Frequency categories are defined as follows:

very common ($\geq 1/10$);

common ($\geq 1/100$ to $< 1/10$);

uncommon ($\geq 1/1\ 000$ to $< 1/100$);

rare ($\geq 1/10\ 000$ to $< 1/1\ 000$);

Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions reported following vaccination with COVID-19 VaccineJanssen

System Organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1\ 000$ to $< 1/100$)	Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$)	Not known (cannot be estimated from the available data)
Immune system disorders				Hypersensitivity ^a ; urticaria	Anaphylaxis ^b
Nervous system disorders	Headache		Tremor		
Respiratory, thoracic and mediastinal disorders		Cough	Sneezing; Oropharyngeal pain		
Gastrointestinal disorders	Nausea				
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system and include batch/Lot number if available.

6 Monitoring of performance of the vaccine in the field

The Applicant proposes 11 studies to further evaluate safety and effectiveness, and to address missing information in the post marketing setting. There are six interventional studies and five non-interventional studies (three safety and two on effectiveness). Safety and effectiveness studies will be conducted only in Europe and USA.

The proposed post-authorization activities don't include studies which cover the populations and special groups that may be commonly found in LMICs supplied with WHO recommended COVID-19 vaccines. Available clinical data may not fully represent all populations. WHO requests some additional studies in the RMP.

6.1 Vaccine efficacy/effectiveness and safety Monitoring

In addition to the collection and monitoring of spontaneous reports and signal detection from healthcare professionals and vaccinees, Janssen has proposed, in the RMP, an Enhanced Active Surveillance. Janssen is considering interventional and non-interventional as additional pharmacovigilance activities:

1. A randomized, double blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COVS.2 (1-dose regimen) for the prevention of SARSCoV-2-mediated COVID-19 in adults aged 18 years and older (VAC31518COV3001). Status: Ongoing. Final report 31 December 2023 (Details of the protocol not available).
2. A randomized, double blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COVS.2 (2-dose regimen) for the prevention of SARSCoV-2-mediated COVID-19 in adults aged 18 years and older (VAC31518COV3009). Status: Ongoing. Final report 30 June 2024 (Details of the protocol not available).
3. A randomized, double blind, placebo-controlled Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COVS.2 in healthy pregnant participants (VAC31518COV2004). Status: Planned. Final report 30 September 2023 (Details of the protocol not available).
4. Interventional trial to evaluate the safety and immunogenicity of Ad26.COVS.2 in immunocompromised patients. Status: Planned. Final report 31 December 2023 (Details of the protocol not available).
5. COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER). Status: Planned. Final report 30 June 2027 (Details of the protocol not available).
6. Post-authorization, observational study to assess the safety of Ad26.COVS.2 using electronic health record (EHR) database(s) in Europe. Status: Planned. Final report 30 June 2024 (Details of the protocol not available).
7. Post-authorization, observational, prospective study to assess the effectiveness of Ad26.COVS.2 in Europe. Status: Planned. Final report 30 June 2024 (Details of the protocol not available).

8. Post-authorization, observational study to assess the safety of Ad26.COVS.2 using health insurance claims and/or electronic health record (EHR) database(s) in the USA. Status: Planned. Final report not yet available (Protocol is under development).
9. Post-authorization, observational study to assess the effectiveness of Ad26.COVS.2 using health insurance claims and/or electronic health record (EHR) database(s) in the USA. Status: Planned. Final report not yet available (Protocol is under development).
10. Co-administration study of Ad26.COVS.2 with seasonal influenza vaccine. Status: Planned. Final report 2023 (Details of the protocol not yet available).
11. The Study to Evaluate Dose Levels and Vaccination Intervals of Ad26.COVS.2 in Healthy Adults Aged 18 to 55 Years Inclusive, Adults Aged 65 Years (VAC31518COVS.2001) including the safety concern of venous thromboembolism. Status: Ongoing. Final report 31 December 2023.

6.2 Programmatic aspects

The programmatic suitability of Covid-19 Vaccine Janssen has been assessed as per the PSPQ WHO recommendations⁹.

Once thawed, the vaccine is ready to use since no reconstitution or dilution is required. The vaccine cannot be refrozen.

Because the vaccine is unpreserved, the intent of the applicant is that each individual vial is used in one single vaccination session or within six hours of opening at 2 - 8 °C, whichever comes first, in line with the WHO Multi-Dose Vial Policy (MDVP).

The proposed vaccine is designed for use in the current COVID-19 pandemic and requires a single dose of 0.5 mL (which is a preferred characteristic according to the WHO Target Product Profiles for COVID-19 Vaccines). If, however, clinical data would show that a second dose is needed to provide long-term protection, the company is considering minimum 2 weeks interval between doses.

The current thermostability profile of the vaccine does not enable it to be matched to a specific Vaccine Vial Monitor (VVM), which is a critical characteristic from the programmatic point of view.

COVID-19 Vaccine Janssen meets most of the mandatory characteristics. Storage condition recommended by the manufacturer goes from 2 years when stored frozen at -25°C to -15°C to 3 months at 2 - 8°C (not exceeding the original expiry date). It does not require an intravenous route of administration and the dose volume is 0.5 mL. However, the vaccine does not meet one mandatory characteristic as it is presented in a 5 doses vial without a preservative.

⁹ [Assessing the programmatic suitability of vaccine candidates for WHO prequalification, Revision 2014](#)

7 SAGE recommendations

The Strategic Advisory Group of Experts on Immunization (SAGE) issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to develop the basis for recommendations once vaccines become authorized. Based on advice provided by SAGE, the initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease.

On 15 March, 2021, SAGE reviewed the available data on COVID-19 vaccine Janssen, also known as Ad26.COV2.S with a specific view of addressing the above-mentioned use scenario. The resulting interim recommendations were released by WHO on 17 March, 2021¹⁰. WHO recommends the use of the vaccine in accordance to the prioritization roadmap in individuals above 18 years of age, without an upper age limit. A one-dose schedule should be used.

WHO currently recommends the use of Ad26.COV2.S according to the Prioritization Roadmap¹¹ (1) even if variants are present in a country. Countries should conduct a benefit-risk assessment according to the local epidemiological situation including the extent of circulating virus variants. WHO will continue to monitor the situation; as new data become available, recommendations will be updated accordingly.

8 Regulatory oversight

The EMA is the regulatory body that has granted the conditional marketing authorization to COVID-19 Vaccine Janssen. WHO has followed up the assessment procedure and rely on EMA's decisions. Therefore, EMA is the regulatory agency of record for this vaccine as per the WHO EUL procedure. The WHO Vaccine Prequalification Team will continue to rely on the regulatory oversight of EMA and will continue fostering participation of WHO experts in EMA's regulatory process.

9 Benefit/Risk Assessment

According to WHO, the COVID-19 pandemic has caused, as of 9 February 2021, over 106 million cases of the disease and over 2.3 million deaths (<https://covid19.who.int/>). COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population and has become a major cause of morbidity and mortality given the inexistence of a vaccine and of proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity be achieved by natural infection have not been borne out because a large proportion of the population remains seronegative, which supports the hypothesis that they are susceptible to the virus. This scenario has been complicated by the recognition of new SARS-CoV-2 variants, whose increased transmissibility

¹⁰ <https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad26.COV2.S-2021.1>

¹¹ WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/m/item/who-WHO-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply>)

and evidence of immune escape mutations has caused concern. The development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

From the efficacy standpoint

One dose of Ad26. COV2.S vaccine demonstrates a VE against moderate to severe/critical COVID-19 at 14 and 28 days post vaccination that is robust and consistent across age groups, between sexes and ethnic groups, and increases against severe/critical COVID-19 with reduction of COVID-19 related hospitalizations (medical intervention) and all- cause mortality (probably highly related to COVID-19 as well).

The onset of protection against the most severe cases begins at Day 7 to increase steadily with time (maintained up to median 58 days). Persistence of VE will become clear with acquisition of new data from ongoing trials. This early onset of protection is important during a pandemic when few subjects are immune, and a high circulation of virus is infecting rapidly the populations.

The VE against all symptomatic COVID-19 is mostly driven by the moderate and severe cases in this spectrum and is therefore not clinically representative. Some variability in VE and immune responses across regions and racial subgroups are noticed. For some subgroups, the numbers of cases were low and the follow-up time short leading to observations that need refinement by collecting more data. Probably circulating strain variance also plays a role.

During the pivotal phase 3 trial, SARS-CoV-2 variants were circulating in the different regions leading to interesting information on cross protection of the Ad26. COV2.S vaccine. The VEs against moderate to severe/critical and severe/critical were comparable in US (Wuhan-Hu1 reference sequence +D614G variant) and Brazil (variant of P2 lineage). In South Africa with a circulating SARS-CoV-2 variant 20H/501Y.V2 (B.1.351 lineage), the VE against the most severe COVID with reduction of COVID hospitalizations and deaths, was as high as in other countries and thus reassuring if this variant spreads globally over time.

From the safety standpoint

Based on the large safety Ad26. COV2.S package, the one dose Ad26. COV2.S demonstrates an acceptable safety and reactogenicity profile in adults including older subjects and adults with comorbidities associated with increased risk of progressing to severe COVID-19.

Reactogenicity (vaccination site pain, fatigue, headache, myalgia) is mild to moderate and transient with a trend to less reactogenicity in older subjects (≥ 60 yrs.). Antipyretics were used more frequently after Ad26. COV2.S because of fever, occurring mostly in younger age group. None of the deaths (19) were considered to be related to the study vaccine.

No indication of any evidence of VAED including VAERD was observed in the clinical data package (induction of high level of neutralizing antibodies and a Th1-skewed CD4 cellular response) which confirms the nonclinical observations in Syrian hamsters and NHP challenge models that the theoretical risk of VAED with Ad26. COV2.S is low.

Current data set does not allow strong conclusion on any impact of pre-existing Ad26-neutralizing antibody titers on safety or efficacy of one dose Ad26. COV2.S vaccine.

Current data sets on breastfeeding women, pregnant women, pediatric population, frailty population, concomitant administration with other vaccines, and HIV population are incomplete or not existing to date to draw conclusions on safety or efficacy of one dose Ad26. COV2.S vaccine.

This acceptable Ad26. COV2.S safety profile is further supported by a large Janssen's AdVac-based vaccines safety database including 26 studies, 4.874 participants with a follow-up duration between 6 months and 4.5 years without any long-term safety issue identified.

In conclusion, one dose COVID-19 vaccine can support faster uptake in a population than 2 doses with immediate positive impact on reduction of disease and mortality even if VE of one dose is lower than 2 doses (*Paltiel - Ann Intern Med 2021 Jan 5;M20-7866 - Speed Versus Efficacy: Quantifying Potential Tradeoffs in COVID-19 Vaccine Deployment*).

The one dose Ad26. COV2.S vaccine data package is in line with this modelling conclusion. The single dose is highly efficacious against the severe/critical COVID19 cases, in prevention of hospitalization and case fatalities related to COVID-19, across all ages and countries, and is effective against newly emerging strains that were circulating during the phase III studies. The VE against moderate to severe/critical COVID-19 is strong.

The favorable storage conditions and the single dose regimen will simplify deployment of vaccination campaigns.

The Ad26. COV2.S vaccine has an acceptable reactogenicity and safety profile.

The long-term safety of the vector component of this vaccine is supported by robust platform data for all Ad26-based vaccines.

The efficacy, immunogenicity and safety data presented support a favorable benefit-risk profile for Ad26. COV2.S vaccine in the indication of active immunization to prevent COVID-19 in adults \geq 18years of age.

10 Conclusion

Considering the public health need to halt COVID-19 morbidity and mortality and to continue immunizing the world's population to the largest extent possible, the introduction of new vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on assessment of the available evidence, the TAG finds that sufficient data is available on Janssen COVID-19 vaccine for an EUL recommendation, subject to the post-listing commitments as indicated in the below sections.

Should new evidence become available that change the benefit-risk assessment (e.g. as a result of the new variants) the EUL recommendation could be reconsidered.

10.1 Quality (CMC) perspective

Based on the outcome of the review of the quality data provided by the applicant, the listing for emergency use of the Covid-19 Vaccine Janssen can be granted. It is concluded that no major concerns exist to list the vaccine.

However, there is specific information that should be provided as post-listing commitments:

1. Considering that proposed stability testing protocols are acceptable, product-specific stability data needs to be generated for the DS and for the DP and must be provided as it becomes available.
2. As part of the continued process verification, the applicant should report process data of detected critical unplanned departures from current designed and controlled processes.
3. The applicant should provide the type of monitoring device that will be used for the international shipping of the vaccine.
4. Because the vaccine is unpreserved, the intent of the applicant is that each individual vial is used in one single vaccination session or within six hours of opening at 2 - 8 °C, whichever comes first, in line with the WHO Multi-Dose Vial Policy (MDVP). Therefore, the proposed WHO Package Leaflet should include this programmatic condition.
5. As part of the Post-Approval Change Management Protocol (PACMP), the applicant should provide WHO:
 - a) The corresponding data after the introduction of additional production sites to increase manufacturing capacity and availability.
 - b) Data to support the scaling up of the manufacturing process, either for the DS or the DP.
 - c) Data to support and to demonstrate comparability of DS and DP, resulting of actions to increase the manufacturing capacity (e.g., addition of sites, scale up).

10.2 Clinical perspective

From the clinical point of review the TAG recommended that an EUL may be granted by WHO to Janssen COVID-19 Vaccine provided that Janssen commits to providing the following requested information post-EUL as soon as such information becomes available:

1. The applicant should submit to WHO further interim analyses and the final clinical study reports of the ongoing studies (COV3001, COV3009, COV2001, COV1002 and COV1001) once they are completed.
2. Once available any relevant data coming from post EUL effectiveness studies should be shared with WHO, as this might change the benefit/risk profile of the vaccine in this population (see pharmacovigilance plan below).
3. The applicant should continue to investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy of the vaccine against severe disease

caused by emerging new SARS-CoV-2 variants. This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.

4. The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine.
5. The RMP should include/address the following:
 - Safety specifications:
 - Potential risks: text should be aligned with the table in section 3.4.3 and add *programmatic error*.
 - Missing information: text should be aligned with the table in section 3.4.3 and add *use in paediatric population <18 years of age, and impact of the emergence of variants on vaccine efficacy/effectiveness and safety*.
 - *Interaction with other vaccines and interchangeability* should be considered separately from each other.
 - Pharmacovigilance plan
 - *The applicant is requested to submit the monthly reports mentioned in the RMP and the PSUR every 6 months. Janssen is requested to ensure that they receive available data from all routine pharmacovigilance activities in all WHO regions.*
 - *The applicant is requested to conduct non-interventional study(ies) for effectiveness, as part of the additional pharmacovigilance activities, in other WHO regions (LMICs). The effectiveness study(ies) should be conducted in LMICs, in particular in Asia and in African countries where no clinical studies were conducted. This request is additional to the 11 studies proposed by the applicant.*
 - *A summary of the protocol should be part of an updated version of the RMP.*
 - Risk minimization activities
 - *A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.*