11 March 2021
EMA/158424/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COVID-19 Vaccine Janssen

Procedure No. EMEA/H/C/005737/0000

Note

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

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List of abbreviations

Ab	antibody
ACE-2	angiotensin-converting enzyme 2
ACE2	angiotensin-converting enzyme 2
Ad26	adenovirus type 26
Ad26	Adenovirus Serotype 26
Ad26.COV2.S	Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein
ADCP	antibody-dependent cellular phagocytosis
ADEM	acute disseminated encephalomyelitis
AdVac	adenoviral vaccine
AE	adverse event
AEFI	adverse event following immunisation
AESI	adverse event of special interest
AEX	Anion exchange chromatography
AEX	Anion exchange chromatography
AF4 MALS	Asymmetric flow field-flow fractionation with multi-angle light scattering detection
AR	adverse reaction
AS	Active substance
BARDA	Biomedical Advanced Research and Development Authority
BMI	body mass index
BOD	burden of disease
BSE	Bovine spongiform encephalopathies
CBER	Center for Biologics Evaluation and Research
CCIT	Container closure integrity tests
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMA	Critical material attributes
cMA(A)	Conditional Marketing Authorisation (Application)
CMC	Chemistry, Manufacturing and Controls
CMV	Cytomegalovirus

CO	clinical overview
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019, caused by SARS-CoV-2
CoVPN	COVID-19 Prevention Network
CPPs	Critical process parameters
CQA	Critical quality attributes
CSR	clinical study report
CT	clinical trial
DLS	Dynamic light scattering
DNA	deoxyribonucleic acid
DRM	Development reference material
DSMB	Data Safety Monitoring Board
DVT	deep vein thrombosis
EBOV	*Zaïre ebolavirus*
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
ELISA	Enzyme linked immunosorbent assay
ELISpot	enzyme-linked immunospot assay
EMA	European Medicines Agency
EOSL	End-of-shelf-life
EU	ELISA units
EU	Endotoxin units
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FOIA	Freedom of Information Act
FP	Finished product
GCP	Good Clinical Practice
GM	geometric mean
GMC	geometric mean concentration
GMO	Genetic modified organism
GMOs	Genetically modified organisms

GMP	Good Manufacturing Practice
GMP	Good manufacturing practise
GMS	Global Medical Safety
GMT	geometric mean titer
GSDR	Global Safety Database Repository
HBCD	2-hydroxypropyl-β-cyclodextrin
HCP	Host cell protein
HEK	Human Embryonic Kidney Cells
HER	Human embryonal retina
HIV	human immunodeficiency virus
IC50	50% inhibitory concentration
ICH	International Council for Harmonisation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
ICU	intensive care unit
ID-PCR	Identity polymerase chain reaction
IFN	interferon
IL	interleukin
IM	intramuscular(ly)
IND	Investigational New Drug
IPC	In-process controls
iPSP	Initial pediatric study plan
IU / Inf.U.	Infectious Units
LC-MS	Liquid chromatography mass spectrometry
LOD	limit of detection
LVHD	Large volume high density
MAAE	medically-attended adverse events
MALS	Multi-angle light scattering
MCB	Master cell bank
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
MHRA	Medicines and Healthcare Products Regulatory Agency
MIS	multisystem inflammatory syndrome

MRU	Medical Resource Utilisation
MS-PP	Mass spectrometry based semi-quantitative protein profiling
MVS	Master virus seed
n/a	not applicable
nAb	neutralising antibody
NGS	Next-Generation Sequencing
NHP	non-human primates
NIH	National Institutes of Health
NLT	Not less than
NPTII	Neomycin phosphotransferase II
OWS	Operation Warp Speed
PACMP	Post-approval change management protocol
PAR	Proven acceptable ranges
PBMCs	peripheral blood mononuclear cells
PC	Polycarbonate
PCR	polymerase chain reaction
PCR	Polymerase chain reaction
Ph. Eur.	European Phamacopoeia
PPI	per protocol immunogenicity set
PPQ	Process performance qualification
PRM	Primary reference material
PV	Process verification
QC	Quality Control
QPA	Quantitative PCR based potency assay
QTPP	Quality Target Product Profile
RCA	Replication competent adenovirus
RCB	Research cell bank
ResMat	Research material
RM	Reference material
RNA	ribonucleic acid
RP-HPLC	Reversed phase high performance liquid chromatography
RP-UPLC	Reverse-phase ultra-high-performance liquid chromatography
RSF	Residual seal force

RSV	respiratory syncytial virus
RT-PCR	real-time reverse-transcriptase polymerase chain reaction S Spike
S	Spike
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAWP	Scientific Advice Working Party
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SmPC	summary of product characteristics
SmPC	Summary of the Products Characteristics
SMQ	standard MedDRA query
SOC	System Organ Class
SSG	Statistical Support Group
SV-AUC	Sedimentation velocity analytical ultracentrifugation
TGE-ELISA	Transgene expression enzyme-linked immunosorbent assay
Th(1/2)	T helper (cells) (type 1/type 2)
TMB	3,3,5,5-tetramethylbenzidine
TSE	Transmissible spongiform encephalopathies
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VE	vaccine efficacy
VNA	virus neutralisation assay
Vp	virus particles
VP	Viral particle or virus particle
WCB	Working cell bank
WHO	World Health Organisation
WHO	World Health Organization
WRM	Working reference material
Wt	wild-type

wtVNA	wild-type virus neutralisation assay
WVS	Working virus seed
yoa	years of age

1. Background information on the procedure

1.1 Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 15 February 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for COVID-19 Vaccine Janssen, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 July 2020.

The applicant applied for the following indication: '*COVID-19 Vaccine Janssen is indicated for active immunisation 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*.'

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0059/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0059/2021 was not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned regulation.

New active Substance status

The applicant requested the active substance adenovirus type 26 encoding the SARS-CoV-2 spike

glycoprotein (Ad26.COV2-S) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
24 April 2020	EMEA/H/SA/4470/1/2020/II	*Dr Jens Reinhardt, Dr Walter Janssens*
4 May 2020	Clarification Letter EMEA/H/SA/4470/1/2020/II	*Dr Jens Reinhardt, Dr Walter Janssens*
9 July 2020	EMEA/H/SA/4470/1/FU/1/2020/III	*Dr Ingrid Schellens, Dr Walter Janssens*
27 November 2020	EMA/SA/0000047617	*Dr Johannes Hendrikus Ovelgonne, Prof Brigitte Schwarzer-Daum*

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The qualification of cell bank system
- Specifications and controls for cell bank system, virus seed system, active substance (AS) and finished product (FP)
- Comparability assessment between phase 3 clinical material and commercial vaccine
- AS and FP process validation approach
- Implementation of new AS and FP manufacturing sites
- The approach to define the Shelf Life for the final product
- Preclinical data requirements before first in man
- The design of an embryo-foetal and pre- and postnatal development study in the rabbit
- Nonclinical and clinical package to support the start of the Phase 3 efficacy study
- The design of the Phase 2 (VAC31518COV2001) and the Phase 3 study (VAC31518COV3001)
- The timelines to initiate paediatric studies and submit a paediatric investigation plan

Compliance with Scientific Advice

In general, the applicant has taken into account the advice and comments provided by the CHMP on the quality-related issues. More particularly, the control strategy and specifications proposed by the applicant in the MAA are largely in line with the recommendations provided.

Regarding the pre-clinical development, points raised were the use of platform data to support clinical development in the absence of studies with an insert-specific vector, timing of Ad26.COV2.S repeat-dose toxicity study, design and timing of EFD-PPND study, nonclinical pharmacology package to support clinical development at different stages, and platform data on biodistribution to support MA in the absence of insert-specific data. The submitted data are not in conflict with the provided advice.

The applicant has sought scientific advice on the clinical data needed to proceed with the Phase 3 study (VAC31518COV3001) as well as different aspects of the design of the Phase 2 (VAC31518COV2001) and the Phase 3 studies. The points discussed during the SA are reflected in the AR where appropriate.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke Co-Rapporteur: Sol Ruiz

The appointed co-rapporteur had no such prominent role in scientific advice relevant for the indication subject to the present application.

The CHMP confirmed eligibility to the centralised procedure on	28 July 2020
The ETF recommended to start the rolling review procedure on	26 November 2020
The applicant submitted documentation as part of a rolling review on non-clinical and clinical data to support the marketing authorisation application	27 November 2020
The procedure (Rolling Review 1) started on	01 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	07 January 2021
PRAC discussions took place on	12 January 2021
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	13 January 2021
ETF discussions took place on	14 January 2021
Adoption of first Interim Opinion (Rolling Review 1 [non-clinical, clinical and RMP]) via 24 hour written procedure on	15 January 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	21 Jan 2021

The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 January 2021
BWP discussions took place on	27 January 2021
ETF discussions took place on	28 January 2021
Adoption of second Interim Opinion (Rolling Review 1 [Quality-ERA-NAS]) via written procedure on	1 February 2021
The applicant submitted documentation as part of a rolling review (Rolling Review 2) on non-clinical data to support the marketing authorisation application	22 January 2021
The procedure (Rolling Review 2) started on	25 January 2021
The Rapporteurs circulated the Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	15 February 2021
ETF discussions took place on	16 February 2021
Adoption of third Interim Opinion (Rolling Review 2) via written procedure on	22 February 2021
The application for the conditional marketing authorisation was formally received by the EMA on	15 February 2021
The procedure started on	16 February 2021
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: 1. Emergent Manufacturing Operations Baltimore LLC, 5901 East Lombard Street, Baltimore, MD 21224, USA (active substance manufacture) 2. Grand River Aseptic manufacturing (GRAM), Grand Rapids MI, 49504-6426, USA (finished product manufacture) 3. Catalent Indiana LLC, 1300 Patterson Drive Bloomington IN 47403, USA (finished product manufacture)	 1. 1st-4th February 2021 2. 25th-29th January 2021 3. 22nd February-1st March 2021
The CHMP rapporteur's and co-rapporteurs Assessment Reports were circulated to all CHMP, PRAC, BWP, peer reviewer and ETF on	4 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all CHMP, PRAC and ETF on	4 March 2021
ETF discussions took place on	8 March 2021
The CHMP rapporteur's and co-rapporteurs updated assessment reports were circulated to all CHMP, PRAC, BWP, peer reviewer and ETF on	9 March 2021
BWP extraordinary meeting was held on	9 March 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary PRAC meeting on	9 March 2021

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to COVID-19 vaccine Janssen on	11 March 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

End of December 2019, World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020 the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally and on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to ECDC, histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 01 March 2021, there have been over 113 million confirmed cases of SARS-CoV-2 infection globally with approximately 2.5 million deaths resulting from infection and subsequent coronavirus disease (COVID-19). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities.

Increasing age is another risk factor for severe disease and death due to COVID-19. European countries that have established surveillance systems in long-term care facilities (LTCF) have reported that 5-6% of all current LTCF residents died of COVID-19, and that LTCF residents accounted for up to 72% of all COVID-19 related deaths.

Individuals with high risk of exposure to SARS-CoV-2 due to occupation include healthcare and frontline workers.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other

coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation and diagnosis

The severity of COVID-19 varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks. Prolonged prothrombin time and elevated C-reactive protein levels on admission to the hospital are associated with severe course of COVID-19 and with a transfer to ICU.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins.

These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for vaccines able to prevent or mitigate COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. Although three vaccines for prevention of COVID-19 were approved recently, there is still an important need for additional vaccines to meet global demands.

About the product

COVID-19 Vaccine Janssen (also referred to as Ad26.COV2.S) is a monovalent, recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) spike (S) protein.

Wild-type adenovirus serotype 26 (Ad26) consists of non-enveloped virions, which encode the adenoviral proteins. The dsDNA molecule is encapsulated by an icosahedral protein structure. The recombinant Ad26 vector Ad26.COV2.S contains a transgene which encodes a modified full-length SARS-CoV-2 spike (S) protein with stabilizing modifications, i.e. 2 amino acid changes in the S1/S2 junction that knock out the furin cleavage site, and 2 proline substitutions in the hinge region.

Following administration of Ad26.COV2.S, the spike glycoprotein of SARS CoV 2 is expressed, stimulating an adaptive humoral and cellular immune response.

Ad26.COV2.S is administered intramuscularly as a single dose of 0.5 mL ($5x10^{10}$ vp, corresponding to not less than 8.92 $\log_{10}$ infectious units).

Proposed indication: '*COVID-19 Vaccine Janssen is indicated for active immunisation 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.'

The same Adenovirus type 26 (Ad26) vector encoding the glycoprotein (GP) of the Ebola virus Zaire (ZEBOV) Mayinga strain has been approved in Europe through Centralised Procedure (Zabdeno, INN: ebola vaccine rDNA, replication-incompetent; Procedure No. EMEA/H/C/005337/0000).

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.

According to the applicant, the efficacy, immunogenicity and safety data presented in their application support a favourable benefit-risk profile for Ad26.COV2.S in the proposed cMA indication, i.e. for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults ≥18 years of age.

This is based on evidence from the ongoing pivotal Phase 3 study COV3001 which examines the efficacy, safety, and immunogenicity of a single dose of Ad26.COV2.S in a diverse adult population ≥18 years of age, including adults ≥60 years of age. The applicant stated that the results for the primary analysis, performed after at least 2 months (8 weeks) of follow-up indicate that Ad26.COV2.S is effective against symptomatic COVID-19 and both co-primary endpoints of the study were met. Vaccine efficacy (VE) (adjusted 95% confidence interval [CI]) for the co-primary endpoints against molecularly confirmed moderate to severe/critical COVID-19 in participants who were seronegative at

the time of vaccination was 66.9% (59.03; 73.40) when considering cases with onset at least 14 days after vaccination and 66.1% (55.01; 74.80) when considering cases with onset at least 28 days after vaccination, with consistent efficacy across age groups.

In addition, the applicant stated that Ad26.COV2.S is highly effective in the prevention of severe/critical COVID-19, particularly in prevention of hospitalisation and death, across all countries and all ages. Vaccine efficacy (adjusted 95% CI) against molecularly confirmed severe/critical COVID-19 with onset at least 14 days after vaccination was 76.7% (54.56; 89.09) and increased to 85.4% (54.15; 96.90) at least 28 days after vaccination. Vaccine efficacy against COVID-19 related hospitalisation (including ICU admission, mechanical ventilation and ECMO) was 93.1% (95% CI: 72.74; 99.20) at least 14 days after vaccination and was 100.0% (95% CI: 74.26; 100.0) at least 28 days after vaccination.

Finally, according to the applicant, there were no COVID-19-related deaths reported in the Ad26.COV2.S group compared to 5 COVID-19-related deaths reported in the placebo group. Ad26.COV2.S, given as a single dose, is found to have an acceptable safety and reactogenicity profile in adults ≥18 years of age and did not raise safety concerns in any of the assessed populations that are reflective of the target groups for vaccination, including adults ≥60 years of age and adults with comorbidities (including comorbidities associated with an increased risk of progressing to severe/critical COVID-19).

- It is likely that the applicant will be able to provide comprehensive data.

The applicant intends to provide a comprehensive post-marketing plan which is proposed to generate additional data on long-term follow-up and in populations not yet studied. These data will be submitted as they become available.

- Unmet medical needs will be addressed.

According to the applicant, despite 3 vaccines approved in the EU, the need for additional vaccines remains high in the EU and globally as the virus continues to spread, with highly transmissible variants continuing to emerge around the globe. The Janssen COVID-19 vaccine candidate, being single-dose, easily transportable and stored, and compatible with standard vaccine distribution channels could aid to the further enhancement of the response, to control this pandemic. In addition, Ad26.COV2.S is highly effective in the prevention of severe/critical COVID-19 caused by newly emerging strains, such as the 20H/501Y.V2 strain first observed in South Africa and the P.2 variant first observed in Brazil. This finding is especially reassuring since it can be expected that more variants will occur over time.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the applicant, a single dose of Ad26.COV2.S is effective against all symptomatic COVID-19. Use of this vaccine could help to control the pandemic, to reduce the burden of disease and relieve pressure on the health care infrastructure, in view if its high efficacy in prevention of severe/critical COVID-19, especially hospitalisation and death. In addition, the favourable storage conditions and single dose regimen will simplify deployment of vaccination.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as a multidose suspension for injection containing not less than 8.92 $\log_{10}$ Inf.U (infectious units) per 0.5 mL dose, of Ad26.COV2-S (recombinant), the adenovirus type 26 vector encoding the SARS-CoV2 spike glycoprotein, as active substance (AS).

Other ingredients are: 2-hydroxypropyl-β-cyclodextrin (HBCD), citric acid monohydrate, ethanol, hydrochloric acid, polysorbate-80, sodium chloride, sodium hydroxide, trisodium citrate dihydrate and water for injections.

The product is available in a 2.5 mL multidose vial presentation (5 doses) in a 10-vial pack. The type I glass vials have a chlorobutyl stopper with fluoropolymer coated surface, aluminium crimp and blue plastic cap.

2.2.2. Active substance

General information

The active substance, Ad26.COV2.S, is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein.

Wild type adenovirus type 26 consists of non-enveloped virions, between 80 and 100 nm in diameter, each containing a single linear molecule of dsDNA of approximately 35 kbp which encode the adenoviral proteins. The dsDNA molecule is encapsulated by an icosahedral protein structure consisting of the structural proteins II (hexon), III (penton), IV (fibre), VI, VIII, IX, and IIIa. Core proteins V, VII, and X and the terminal protein are directly associated with the DNA molecule. The virus structure is shown in Figure 1.

The recombinant Ad26 vector, Ad26.COV2.S, is replication incompetent after administration due to deletions in the E1 gene (ΔE1A/E1B). The E1 deletion renders the vector replication-incompetent in noncomplementing cells such as human cells. In Ad5 E1 complementing cell lines (e.g., HEK293, PER.C6 TetR and HER96 cells lines) the virus can be propagated. In addition, a part of the E3 gene region has been removed (ΔE3) to create sufficient space in the viral genome for insertion of foreign antigens and the Ad26 E4 orf6 has been exchanged by the Ad5 homologue to allow production of replication-incompetent Ad26 vectors in Ad5 E1 complementing cell lines.

The Ad26.COV2.S vector contains a transgene in the ΔE1A/E1B region which encodes a modified full-length SARS-CoV-2 spike protein with stabilizing modifications (Figure 2). The wild-type full-length S gene information (NCBI reference: YP_009724390.1) was obtained from a SARS-CoV-2 clinical isolate.

During production of the recombinant vector the expression of the S antigen is silenced by the producing cell line (PER.C6 TetR cells). After administration of the vaccine, the S antigen will be expressed in humans which will lead to an immune response.

Figure 1: Schematic Representation of the Structure of the Ad26 Virion

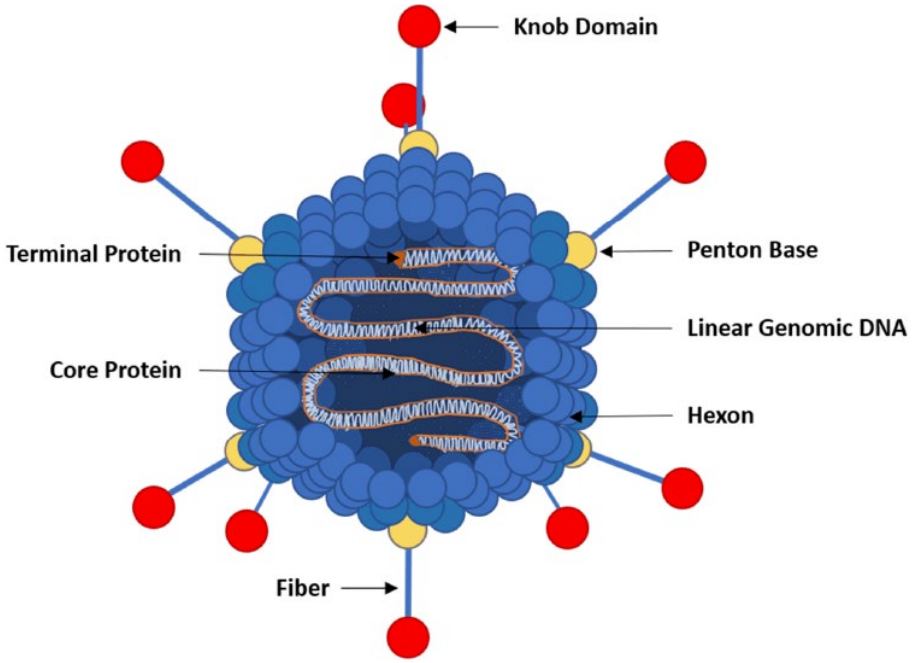


Figure 2: Schematic Representation of the Ad26.COV2.S Vector Genome

Manufacture, process controls and characterisation

The AS is manufactured by Janssen Vaccines & Prevention B.V. (Leiden, NL), Janssen Biologics B.V. (Leiden, NL), and Emergent Manufacturing Operations Baltimore LLC (Baltimore, USA).

A Major objection was raised during the procedure for the absence of certificates of GMP compliance for Janssen Biologics B.V. (Leiden, NL) and Emergent Manufacturing Operations Baltimore LLC (Baltimore, USA). The certificates have now been issued and the major objection resolved. All relevant active substance sites have valid manufacturing authorisations or valid GMP certificates as appropriate.

Description of manufacturing process and process controls

The AS manufacturing process consists of ten stages: 1) pre-culture 2) cell expansion 3) virus production 4) lysis 5) DNA precipitation; 6) clarification 7) anion exchange chromatography (AEX) chromatography 8) polishing and buffer exchange 9) final adjustment and fill and finally 10) freezing of the AS.

Each preculture train (from large volume high density (LVHD) bag thaw through 10 L wave-mixed culture used for inoculation of stage 2) originates from a single LVHD bag and is used to produce one batch of AS.

All steps of the AS manufacturing process are described in detail. The process starts with thawing of a vial of the cell substrate. Cells are expanded and then inoculated with the recombinant adenoviral construct. After virus production the cells are lysed and virus is collected. Purification steps include a DNA precipitation step, a clarification, an anion exchange chromatography step and diafiltration. The diafiltered product is then formulated and undergoes a 0.2 µm filtration before filling in polycarbonate bottles. No reprocessing is claimed. The active substance is stored below -40°C.

As regards the control strategy, the manufacturing process is controlled using process parameters and in-process controls. Critical process parameters (CPPs) have been provided for the AS manufacturing process which has been verified during AS process performance qualification (PPQ). The proposed operating ranges for the CPPs are acceptable.

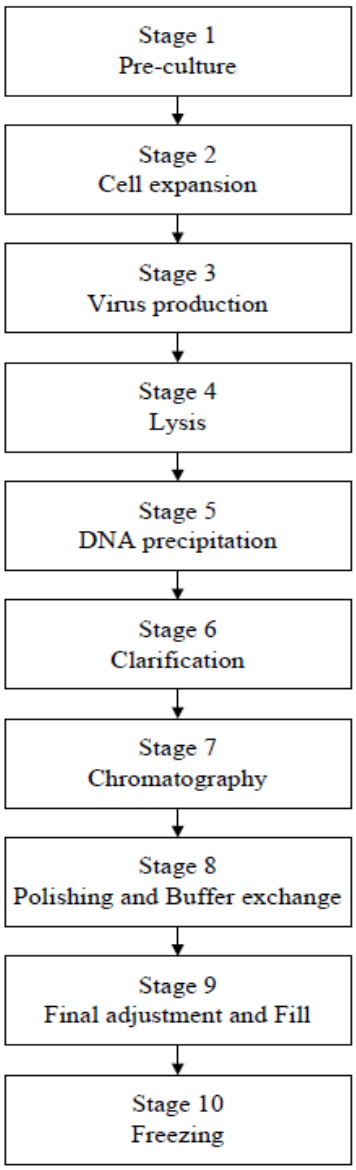
Both a small scale process at Janssen Vaccines & Prevention B.V. (Leiden, NL), and a large scale process, at Janssen Biologics B.V. (Leiden, NL) and at Emergent Manufacturing Operations Baltimore LLC (USA), are included in the marketing authorisation application. The small scale process will be used for the initial commercial AS batches. Both small and large scale processes use tiered virus seed systems (including master virus seed (MVS), working virus seed (WVS) and inoculum). All virus seed material originates from the same MVS batch.

Quality of process intermediates is adequately controlled by in-process controls. Any excursion outside of the defined ranges (action limits) will be investigated. A distinction is made between in-process controls (IPC) with strict acceptance criteria and IPC with predefined instructions. IPC results have to comply with acceptance criteria. The methods used for IPC and the method qualifications have been described.

The manufacturing process is performed in a production facility at controlled room temperature. Maximum process durations and processing temperatures are defined. The combination of hold time(s) and processing time(s) should not exceed the maximum process duration. Upon request, the applicant provided data for lifetime and sanitisation procedures for the anion exchange chromatography material.

See Figure 3 for a flowchart of the AS manufacturing process.

Figure 3: AS Manufacturing Process Overview



Control of materials

Raw materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. All materials have been described in detail. Compendial raw materials are tested in accordance with the corresponding monograph. For non-compendial raw materials, adequate specifications are in place to control their quality. Composition of media has been provided. No raw materials of human or animal origin are used in the AS manufacturing process.

During establishment of the virus seed, bovine serum has been used which was compliant to the effective version of EMA/410/01 (European Commission: Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products), and thus does not pose any risk for transmission of transmissible spongiform encephalopathies/bovine spongiform encephalopathies (TSE/BSE).

Benzonase, which is used during AS manufacturing, is produced in bacteria. The fermentation medium contains casein hydrolysate that is produced from bovine milk sourced from healthy animals from

Australia and New Zealand. The material complies with the Note for Guidance EMEA/410/01 Rev. 3 (TSE). Casein hydrolysate is sterile filtered before its introduction into the fermentation medium. The latter itself is sterilised additionally in the fermenter at 121°C, 1 bar for 35 min. Accordingly, there are no risks with regards to extraneous agents (viral or microbial) contamination.

Cell bank system

The PER.C6 cell line is used for virus production. The PER.C6 cell line was derived from human embryonal retina (HER) cells, which were rendered immortal by transfection with the linearised pIG.E1A.E1B plasmid. The construction of the PIG.E1A.E1B plasmid was extensively described. The preparation of both, adherent and suspension PER.C6 cell banks as well as the generation and selection of the PER.C6 TetR cell line and research cell bank (RCB) are well described. The PER.C6 TetR cell bank system has been documented in detail and is in line with ICH Q5D and ICH Q5A (R1). This cell bank was derived to optimise production of the recombinant virus. The repressor protein, which is expressed by the PER.C6 TetR cells, blocks expression of the SARS-Cov-2 transgene during production of the recombinant adenoviral vector, thereby optimising vector production.

The cell banking system is a tiered system, including MCB, WCB and LVHD. Information on storage and stability testing of cell banks is provided. Extensive testing at different levels (PER.C6 cell bank system and PER.C6 tetR cell bank system) has been performed which confirms that the PER.C6 TetR master cell bank (MCB) and working cell bank (WCB) have been properly qualified. Testing of cell banks for viral and non-viral adventitious agents and screening also for retroviruses has been sufficiently described and is acceptable. Tumorigenicity and oncogenicity studies have been performed on the PER.C6 cell line. It is accepted that repetition of these studies with the PER.C6 TetR cell line is considered not necessary in line with WHO TRS 978 Annex 3 and ICH Q5D. Additional characterisation testing also confirmed correct identity and genetic stability of the cell bank system. The applicant also described the manufacturing of future WCBs and LVHD cells. The proposed testing programme to qualify future WCBs and LVDH cells is deemed adequate.

Virus seed system

The construction of the plasmid pAd26.E1.CMVdel134-TO.COR200007 has been described. The pAd26.E1.CMVdel134-TO.COR200007 is a single genome plasmid which was used to produce the Ad26.COV2.S vector by transfection of this plasmid into PER.C6 TetR cells. To generate the replication incompetent Ad26.COV2.S virus, linearised pAd26.E1.CMVdel134-TO.COR200007 was transfected into PER.C6 TetR cells from PER.C6 TetR RCB N644-076. Two plaque purifications were performed to ensure the single plaque origin of the virus seed stocks. MVS 20E18-04 was prepared by infecting PER.C6 TetR cells with pre-MVS E005872. The crude harvest (MVS 20E18-04) has been stored in cryobags in a freezer below -65°C. WVS 20E20-05 was prepared by infecting PER.C6 TetR cells with MVS 20E18-04. A new WVS 964918 has been prepared for the large scale process. WVS 964918 (large scale) was generated from MVS 20E18-04 by first generating Ad26.COV2.S intermediate virus passage (IVP) 20F11-04, which was subsequently used to generate WVS 964918.

Both small and large scale processed uses tiered virus seed systems. All virus seed material originates from the same MVS batch. Generation of the recombinant virus and production and testing of the MVS and WVS has been described in detail (identity, safety including testing for sterility, mycoplasma, retroviruses for WVS, in vitro adventitious virus assay, replication competent adenovirus (RCA) and viral content). The proposed tests are deemed adequate. Specific tests for human viruses, porcine viruses and MMV were not performed since no materials from human or animal origin were used during generation of the virus seed system (except for irradiated foetal bovine serum). Since bovine serum was used during production of the pre-MVS, possible contamination by highly resistant bovine viruses cannot be fully excluded. Therefore, the applicant has performed additional screening for bovine viruses. The MVS and WVS were characterised for infectivity titre, genetic stability and stable expression of the

transgene. MVS, WVS and AS have identical sequences, demonstrating genetic stability. In addition, AS manufactured by the large scale process using inoculum (which includes additional virus passages) had identical sequences, confirming genetic stability. Correct expression of the transgene was confirmed.

The applicant also described the manufacture of future WVS. The proposed testing programme to qualify future WVS is deemed adequate. The applicant confirms its commitment to implementing the 3Rs principle. The use of in vivo methods to qualify future batches of WCB, LVHD and WVS is not necessary since the manufacture of such materials does not represent any contamination risks that are not already mitigated. The in vivo testing has been removed as a release requirement for future batches of WVS, WCB and LVHD (including testing via end of production cells).

A summary of the validation of the transport of the cell banks and virus seeds to the manufacturing sites has been provided. Transport is properly validated.

Control of critical steps and intermediates

The applicant provided an overview of critical process parameters (CPPs) and in-process controls (IPC). Overall, the control strategy is deemed acceptable. Each IPC is associated with a test method, a sampling location and an acceptance criterion or a predefined instruction. IPC results comply with acceptance criteria. See manufacturing process development section for further details of control strategy development.

Process validation

Process validation has a lifecycle, starting with process development followed by commercial scale process verification/process performance qualification (PV/PPQ) runs and then continues in the form of ongoing process verification throughout routine production. Process validation at commercial scale is carried out to demonstrate that the process is capable of reproducibly manufacturing product meeting quality requirements.

Based on experience with the Ad26 vaccine platform products, critical quality attributes (CQA), critical material attributes (CMA) and CPP have been assigned. The process validation addresses the following: validation of different process steps (Stages 1-10); qualification of process intermediate hold times; control of impurities; consistency of DS; shipping qualification; continued process verification. Furthermore, IPC and release tests were established as part of an initial control strategy. The purpose of process validation is to demonstrate that the manufacturing process meets the acceptance criteria for IPC, release testing, CPP and CMA. Supporting data to confirm these CPPs and CMAs and to define proven acceptable ranges (PAR) are generated during process validation concurrent to Ad26.COV2.S commercial manufacturing.

PPQ data have been provided for the small scale AS process at Janssen Vaccines & Prevention B.V. (Leiden, NL), the large scale AS process at Janssen Biologics B.V. (Leiden, NL) and Emergent Baltimore (USA), including data from AS process verification / process performance qualification (PV/PPQ) (process parameter results, IPC results, impurity removal, batch data and hold times) confirming the validated status of the process at these sites. In addition, process validation for the inoculum performed at Janssen Biologics B.V. (Leiden, NL) was completed through the successful execution of two consecutive PV/PPQ batches. Results from the third PPQ lot should be provided post-approval (**recommendation 1**).

Two active and passive shipping systems are proposed and have been suitably validated for the transport of AS. Qualification data were provided to support the hold times used during AS manufacture. A shipping system has been qualified for the transport of inoculum.

Manufacturing process development

A process control strategy was developed based on extensive AdVac/PER.C6 platform experience and following scientific rationale. Potential CQA, preliminary CPP, and preliminary CMA were established and controlled by different tests: IPC, release, characterisation and stability. The risk for viral contamination, RCA and adventitious agents has been mitigated by performing appropriate testing to starting and raw materials in compliance with applicable regulatory guidance documents, together with appropriate IPC and release tests. The process used to identify critical quality attributes associated with the AS and FP is sufficiently described and explained. A criticality assessment was performed based on the level of severity and the degree of knowledge uncertainty. The CQA identified by the criticality assessment are properly described. A summary of the preliminary CPP and CMA is provided, together with justifications for their criticality.

The history of the process development is summarised. Four process manufacturing variants (S-VAL-1 to S-VAL-4) of the AS manufacturing process have been used for the small scale process and three additional variants (S-VLF-1, S-VLF-2 and S-EME-1) for the large process.

The batches that have been produced for clinical development as well as the current inventory of material produced for commercial use were manufactured at the small bioreactor scale (Janssen Vaccines & Prevention B.V., Leiden, NL). To ensure sufficient supply for commercial use, the applicant has upscaled the process to a bioreactor of large scale at the Janssen Biologics B.V. (Leiden, NL) site and the Emergent Baltimore (USA).

Detailed information has been provided on the equipment used and on the process parameter results and IPC results for the 3 clinical lots and the first commercial AS lots of each of the three commercial sites. Results were highly similar for all process parameters and IPCs for all AS batches produced thus far.

The essential elements of the AS manufacturing process were retained throughout process development. The AS manufacturing process variant S-VAL-2/3 did not change with respect to the manufacturing process variant S-VAL-1, apart from two differences. The introduction of an additional virus seed passage (AS was manufactured from WVS i.e. additional virus seed passage) was qualified by a comparability analysis confirming the absence of any impact on AS quality. Variant S-VAL-1/2/3 were used for Phase 1/2/3 clinical trials; however, these 3 variants can essentially be considered the same process. The introduction of a larger AS storage container is also assessed. Some further process optimisations were introduced for the S-VAL-4 process used for the small commercial batches. A 2-Tier staggered approach has been used to demonstrate comparability between S-VAL-2/3 and S-VAL-4 AS batches. The Tier 1 contains the release testing results and some important characterisation tests. The Tier 2 part of the comparability assessment comprises additional characterisation. Both the results for release tests and characterisation tests were highly similar. Therefore, it can be concluded that the AS lots from the commercial small scale process at Janssen Vaccines & Prevention B.V. (Leiden, NL) are comparable to the lots used in the Phase 3 clinical trials.

Furthermore, as part of the qualification of the large scale process at the Janssen Biologics B.V. (Leiden, NL), a third study was performed to demonstrate comparability between AS from the large scale process and the small scale process (Process Variants S-VAL-4, small scale, and S-VLF-1/2, large scale) and was also designed as a 2-Tier staggered approach. Comparability was demonstrated based on the tier 1 comparability data. Similarly, comparability was also demonstrated between AS from the Emergent (USA) site and AS from the other commercial sites based on tier 1 data. The applicant should provide, upon availability, the tier 2 comparability data to confirm that the large scale AS (from Janssen Biologics B.V. (Leiden, NL) and from Emergent Baltimore (USA)) is comparable to the small scale process material (from Janssen Vaccines & Prevention B.V., Leiden, NL) (**recommendations 2** and **3**).

Characterisation

Characterisation studies were conducted using AS batches and FP batches, including clinical trial material and commercial use lots, investigating capsid composition, particle heterogeneity, virus DNA, biological activity and structure-function relationships.

The AS has been adequately characterised using a range of biochemical, biophysical and biological state-of-the-art methods revealing that the active substance has the expected structure.

In conclusion, the correct expression of adenovirus proteins was confirmed and shown to be consistent. In addition, typical adenovirus particle results were obtained upon biophysical characterisation.

Biological activity: Relative level of transgene expression was measured by transgene expression enzyme-linked immunosorbent assay (TGE-ELISA). Infectivity as determined by quantitative PCR based potency assay (QPA) in release testing showed a strong correlation to the TGE-ELISA characterisation results, supporting that the transgene expression level is sufficiently controlled by infectivity (QPA) in release testing.

Characterisation of virus DNA confirmed the transgene identity and flanking regions. The genomic integrity and stability of Ad26.COV2.S AS was shown upon additional passaging. Furthermore, transgene genetic stability analysis confirmed expression of the transgene and phenotypic stability.

Finally, structure/function relationships were characterised using forced degradation studies which indicated that the major route of degradation of Ad26.COV2.S exposed to thermal stress was virus protein degradation. This degradation led to a linear decrease in potency (on $\log_{10}$ scale) as determined by infectivity and relative transgene expression measurements, indicative of a first order degradation.

Additional characterisation was carried out with the inoculum to determine genetic stability.

Impurities

Process-related impurities have been characterised during clinical development of the current product and also during previous studies performed for other Ad26 viral vectors produced using the same platform technology. Process-related impurities from the AS manufacturing process include cell culture media components and additives, PER.C6 TetR host cell constituents and downstream buffer components. The principles of quality risk management (ICH Q9) were used to identify critical process-related impurities.

From the assessment of 81 impurities, it was concluded that most were non-critical. Only 2 process-related impurities were considered critical, host cell DNA and host cell protein (HCP); these are controlled via the AS specifications.

Upon request, the applicant has provided summaries of the impurity spiking studies. The data demonstrate that the chromatography purification and the various filtration steps result in efficient removal of impurities. All these impurities are reduced by several log units during purification of AS. The level of impurity removal is deemed sufficient.

The applicant has also provided calculations of worst-case situation levels of the different impurities taking into account the reduction obtained by the purification steps. It was shown that all impurities are reduced to sufficiently low levels which do not raise any concerns regarding safety.

Potential product-related impurities include empty or incomplete adenovirus particles, adenovirus aggregates and (fragments of) adenovirus proteins, and post-translationally modified forms of the adenovirus protein. Product-related impurities, were analysed and shown to be low in quantity and consistent between AS batches (regardless of the DS manufacturing scale, small or large).

The stated impurities have been present in product used in clinical trials.

Specification

The release and stability specifications for Ad26.COV2.S AS comprise appropriate physico-chemical tests and tests for identity, purity and potency.

The specification of Ad26.COV2.S AS consists of the following tests: identity by ID-PCR and virus protein fingerprinting by reversed phase high performance liquid chromatography (RP-HPLC); impurities (HCP by ELISA and host cell DNA by qPCR); potency (transgene expression by qualitative ELISA, infectious units, ratio virus particles/infectious units); quantity (virus particles by VP-qPCR), safety (bioburden, bacterial endotoxins, replication competent adenovirus) and general tests (appearance, pH and polysorbate 80 concentration).

The specifications proposed for the AS are deemed acceptable. Upon request during the procedure the applicant has included a release test for replication competent adenovirus (RCA) which is considered an important safety test for a pandemic vaccine virus and required by the Ph. Eur. 5.14.

Upon request the HCP acceptance criterion has been further tightened to an acceptable level. In addition, the infectivity specification has been increased to maintain alignment with the revised FP specification.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Compendial methods were verified to demonstrate that the methods are suitable for use with the current product and that no interference/inhibition occurs.

The specification includes tests for both viral particle (VP) concentration and infectious units (Inf.U) to measure potency.

Transgene expression is measured by an enzyme-linked immunosorbent assay. The qualitative procedure to measure transgene expression confirms that cells infected with Ad26.COV2.S express the transgene protein. Upon request, the applicant provided more information on the source of the recombinant fusion protein, that is used as a primary antibody in the transgene expression assay; specificity of this primary antibody has been demonstrated.

Batch analysis

Satisfactory batch analysis data and additional characterisation test results are provided for clinical AS batches and small scale commercial batches (including PPQ lots), all produced at the Janssen Vaccines & Prevention B.V. small-scale commercial AS manufacturing site (Leiden, NL), for large scale PPQ batches produced at the Janssen Biologics B.V. large scale manufacturing site (Leiden, NL) and for large scale PPQ batches produced at the Emergent Baltimore (USA) site.

Reference materials

The same reference standard is used for AS and FP testing. See FP Reference materials section for more detailed information.

Container closure system

The applicant provided a detailed description of the AS container. An extractables study was performed for the AS container. The data from the extractables study results did not indicate any reason of concern. The container is stated to comply with the European requirements on leachables and extractables outlined in CPMP/QWP/4359/03. The container closure system for the AS is qualified for product shipping,

freezing/thawing and long-term storage. The integrity of the container closure system is validated. A risk assessment was performed which confirmed that additional leachables studies are not required for the AS container.

Stability

A shelf life of AS when the AS is stored frozen was proposed by the applicant.

The proposed shelf life is supported by long term (below -40°C) and accelerated (2-8°C) stability data from other Ad26 viral vectors produced using the same platform technology (> 40 AS lots ranging from 24 months to 48 months stability). These lots were also stored in the same polycarbonate containers as proposed for this product and they were manufactured at the small scale at Janssen Vaccine and Prevention B.V. (Leiden, NL). Given the COVID-19 pandemic and the current circumstances and urgency, this approach is deemed acceptable. The AS is typically very stable when stored below -40°C; no trends are observed during shelf life.

The applicant has placed representative AS lots on stability (real time at -60°C and accelerated at 5°C) in accordance with applicable ICH guidelines. These include clinical and manufacturing lots manufactured at the small scale at the Janssen Vaccine and Prevention B.V. site (Leiden, NL) and large scale lots from the Janssen Biologics B.V. site (Leiden, NL). Since the glass transition temperature of the AS is -34°C, stability studies at the proposed temperature are appropriate to support the storage conditions. AS lots were stored in bottles considered representative of the commercial containers. The proposed stability testing programme is deemed acceptable and includes appropriate stability-indicating parameters. All batches are tested for pH, infectious units, transgene expression, virus particle (vector concentration), and ratio VP/ Inf.U at all timepoints.

Currently 6 months stability data are available for AS lots and 3 months for the small scale commercial lot (manufactured at the Janssen Vaccine and Prevention B.V. site) and for one large scale commercial lot (manufactured at the Janssen Biologics B.V. site). The AS stability studies will be continued until completion at the real-time stability storage condition and at the accelerated stability storage condition. The applicant should provide the AS stability data for representative AS batches (from the small scale production site) when the stability study has been finalised and the results are available (**recommendation 4**). Any confirmed out-of-specification result, or significant negative trend, should however be reported to the EMA. In addition to the three representative small scale AS lots, stability studies have been initiated with large scale commercial AS batches. Results will be provided when the data are available. Finally, the applicant should also initiate stability studies for 3 PPQ AS lots from each of the AS manufacturing sites and from future added sites (**recommendation 4**).

An appropriate shelf-life of the AS and storage conditions were agreed. Stability-monitoring programs for two inoculum batches have also been initiated. A re-test date for inoculum when stored frozen was proposed by the applicant. This date will be extended when the stability studies confirm stability.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

FP composition

The Ad26.COV2.S FP is supplied as a sterile liquid suspension for injection. The FP is intended for administration by the intramuscular route.

Each dose contains not less than 8.92 Log_{10} Infectious Units (Inf.U) and not less than 2.5×10^{10} VP.

The container closure system used for the finished product is a 2R Type I glass vial with a chlorobutyl closure and an aluminium seal with a flip-off cap. Each vial contains an excess fill volume to allow for an extractable volume of 2.5 mL as 5 extractions of 0.5 mL. The FP contains no preservative.

The composition of the FP is shown in Table 1. The AS is already formulated in formulation buffer sterile filtered and filled in 2R Type I glass vials with an excess fill volume for commercial supply batches. No additional excipients are added during the FP manufacture. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

Table 1: Composition of Ad26.COV2.S FP.

Component	Grade[a]	Function
Ad26.COV2.S	Company Standard	Active
Sodium chloride	Ph. Eur., *0193*	Tonicity agent and stabiliser
Citric acid monohydrate	Ph. Eur., *0456*	Buffer agent
Trisodium citrate dihydrate	Ph. Eur., *0412*	Buffer agent
Polysorbate-80	Ph. Eur., *0428*	Stabiliser
2-hydroxypropyl-β-cyclodextrin (HBCD)	Ph. Eur., *1804*	Stabiliser
Ethanol	Ph. Eur., *1318*	Stabiliser
Sodium hydroxide	Ph. Eur., *0677*	pH adjuster
Hydrochloric acid	Ph. Eur., *0002*	pH adjuster
Water for injections	Ph. Eur., *0169*	Diluent

Formulation development

The development of the FP has been described in detail. The formulation composition (excipients, concentrations, pH) of Ad26.COV2.S FP was based on prior knowledge from formulation studies with similar adenoviral vector-based products.

The type of excipients and the quantitative composition of Ad26.COV2.S FP were selected based on early formulation development studies. The selection of the formulation composition was based on the results of formulation screening and optimisation studies performed for Ad26.COV2.S and representative Ad26 platform products and parameters evaluated comprised pH, buffer type, various stabilisers (cryoprotectant, antioxidant and surfactant) and tonicifying agents.

Suitability of the final selected formulation for Ad26.COV2.S FP was demonstrated in product-specific studies demonstrating acceptable stability during refrigerated and accelerated storage. The late stage Ad26.COV2.S FP development consisted of studies designed to evaluate the stability of the formulation during temperature cycling, freeze-thaw stress, mechanical stress (agitation) and thermal stability at elevated temperatures. The conclusions are based on studies on Ad26.COV2.S and representative Ad26 platform products. Overall, the Ad26.COV2.S data obtained in assessments covering the range of conditions described are in agreement with representative Ad26 platform products data and support leveraging of platform data.

Pharmaceutical development

The Quality Target Product Profile (QTPP) is presented with links to defined CQAs. For the CQA identification process, potentially relevant quality attributes were selected based on the QTPP, pre-assessment and prior knowledge of other adeno vectors. Control of FP CQA is based on an integrated strategy including material controls, process parameter limits, IPCs, release and stability testing and GMP/ quality systems. A summary is provided of the criticality identification process and assessments for CPPs. Data supporting proven acceptable ranges (PAR) for CPP and non-CPP (nCPP) are provided.

However, some parameters are still being evaluated and are classified as potentially critical. A final conclusion on the criticality of the potentially critical parameters should be provided upon availability (**recommendation 10**). The justifications of IPC acceptance criteria, including summaries of IPC results during the development and clinical manufacturing batches are provided.

Information was provided on the different process variants used during product development and on the FP batches produced thus far. The differences between the clinical and commercial manufacturing processes are described and includes changes of site, change from single to multi-dose and scale. Information is provided to support equivalence of the clinical trial and commercial formulation buffer composition and manufacture.

Additionally, to evaluate the sensitivity of Ad26.COV2.S FP when exposed to light stress, a study based on the ICH Q1B requirement will be performed. The samples should be tested for potency, turbidity, radius and aggregation (**recommendation 8**).

The AS thawing stage includes storage of AS at the FP manufacturing facility, thawing of frozen AS and an optional refrigerated intermediate hold step.

Comparability

A comparability analysis was performed demonstrating that early clinical material (phase 1/2) was comparable to the FP lots used in the phase 3 trials (study 1). Based on an assessment of the release, IPC and characterisation results of the clinical batches the study 1 conclusions are that the Ad26.COV2.S FP batches produced using the post change manufacturing process variants are comparable to the FP batches produced using the pre change manufacturing process variant. This comparability assessment therefore confirms that the post-change manufacturing process variants introduced do not adversely impact the quality, safety and potency of the Ad26.COV2.S FP batches. A forced degradation study (thermal stress) is ongoing in support of this comparability assessment (**recommendation 9).**

Since some changes have also been introduced in the FP process for commercial production, a comparability analysis has been initiated to compare phase 3 FP lots and future commercial FP lots (study 2). A 2-tiered approach has been proposed by the applicant to demonstrate comparability. According to this approach, initial comparability assessment (tier 1) consists of comparison of release and IPC results. If the release results of both pre- and post-change FP batches are within the commercial specifications, it will be concluded that the initial comparability criteria are met and post-use FP lots will be released for commercial use. This enables timely use of post-change materials to alleviate the high demand due to the COVID-19 pandemic. The tier 1 results have already been provided for the FP PPQ lots from the first FP commercial site and demonstrate that the commercial FP is comparable to the clinical material. Additional characterisation test results (tier 2) should be provided post-approval (**recommendation 6**). In addition, comparability data (tier 1 and tier 2) is requested for the second finished product site to confirm the FP is comparable to the FP from the first commercial site and the clinical material (**Specific obligation 1**). Given the COVID-19 pandemic and the current circumstances and urgency, this approach is deemed acceptable.

Container closure integrity tests (CCIT), residual seal force (RSF) tests and headspace analysis are used to validate the integrity of the container closure system and its ability to prevent the ingress of microbial contamination to the final product. In addition, Ad26.COV2.S FP samples have been tested for RSF at t = 0 and after 3 weeks of storage at -85 ºC confirming integrity of the FP container. Compatibility studies were performed mimicking vaccine administration conditions in the field to ensure that the steps required prior to administration do not impact the quality of the product. Results of studies investigating the compatibility of the Ad26.COV2.S FP with syringes and needles used for intramuscular administration

are presented. Physicochemical and biological stability as well as microbiological safety were assessed. Additionally, microbial growth for the in-use conditions was evaluated in a microbial challenge study.

Container closure system

Detailed information was provided on the multi-dose FP container closure system, which contains 5 doses of the FP. The container closure system used for the FP is a 2R Type I glass vial closed with a latex-free rubber stopper (chlorobutyl with fluoropolymer coated surface), aluminium crimp and blue plastic cap. All relevant components (glass vials and rubber stoppers) comply with applicable Ph. Eur. guidance.

Container closure integrity of the FP container was demonstrated. Extractables and leachables studies were performed (or are ongoing). The extractables study did not reveal any compounds of concern as regards safety. The applicant has provided data from an extractables study performed for Zabdeno (same container, vial and stopper). These data did not indicate any compounds of concern. Results from the leachables studies should be provided post-approval (**recommendation 11**).

Manufacture of the product and process controls

The FP is manufactured at different manufacturing sites. Batch certification is performed at Janssen Pharmaceutica N.V. (Beerse, BE) or Janssen Biologics B.V. (Leiden, NL). All sites have appropriate GMP certification. A detailed listing of test sites and associated testing is stated in the dossier.

A major objection regarding GMP status was raised for three FP sites however, valid proof of GMP compliance has now been provided for these sites. The major objection is resolved.

The applicant has proposed an additional FP release testing site for sterility and endotoxin. However, qualification of this site is currently ongoing and is expected to be finalised in May 2021. Therefore, the applicant has requested a time-limited exemption allowing reliance on FP release testing for sterility and endotoxin conducted in registered sites that are located in a third country. This approach is acceptable. The length for the QC testing site exemption has been clearly defined (until 30 June 2021) and it concerns compendial tests (endotoxin and sterility). Suitability testing will be performed according to pharmacopoeial requirements for method transfer qualification (see **Product Information Annex II.A**).

Description of manufacturing process and process controls

The FP manufacturing process consists of several steps. First, the AS is thawed, pre-filtered, pooled and diluted with pre-filtered formulation buffer. The formulated bulk is homogenised, sterile filtered in-line (two 0.2µm filters connected in series) and aseptically filled into vials, stoppered and capped. Filling is done immediately after sterile filtration. The sterile filtered bulk is not stored. Subsequently, the vials are visually inspected, frozen, labelled and packed.

All steps of the FP manufacturing process at the proposed FP manufacturing sites have been described and information on CPPs and IPCs was provided. The proposed CPPs and IPCs are deemed adequate and sufficient to control the FP process.

Prior to the start of sterile in-line filtration, both sterilising filters are tested to ensure filter integrity, and a bioburden sample is taken from the holding vessel.

The minimum and maximum FP batch size has been defined for the proposed FP manufacturing sites. Hold times are defined. The formulation buffer used in the commercial FP manufacture is made at the commercial manufacturing site as part of the FP manufacturing process.

Process validation and/or evaluation

The validation of the manufacturing process for the Ad26.COV2.S FP consists of several steps: (1) validation of process steps, (2) validation of hold times during manufacturing process and (3) validation of media fills.

Process verification and process performance qualification (PV/PPQ) studies have been performed for the FP sites. The process validation for manufacture of Ad26.COV2.S FP consisted of three successful validation runs performed at the minimum, intermediate and maximum FP batch sizes. For each of the process validation runs, the IPC and FP product release met their predefined acceptance criteria and FP release specifications, respectively. The results presented in this section demonstrate that the Ad26.COV2.S FP manufacturing process as executed at the commercial manufacturing site is under control and produces final FP of consistent quality that meets specifications. Continued process verification (CPV), will be performed to assure that the FP process remains in a state of control during commercial manufacture. The FP manufacturing process at the site is adequately validated. Some additional characterisation data to confirm homogeneity and the hold times should be provided when available (**recommendation 7**).

With regards to the second FP manufacturing site, batch data of the 3 PPQ lots were provided. All results were compliant with the FP specifications and also highly similar to release test results from phase 3 clinical lots and batches from the first site. However, the complete data have not been provided. Therefore, the applicant is requested to provide the full FP PPQ data from the 3 representative FP lots from the second site (including hold times). In addition, comparability data (tier 1 and tier 2) are requested to confirm that the FP from this site is comparable to the FP from the first commercial site and consequentially also confirm comparability with clinical material (**specific obligation 1**). This approach is acceptable in the context of the COVID-19 pandemic public health emergency.

The applicant has submitted an updated section 3.2.S.2.5 on shipping validation including information on air transport. All shipping routes are described including air transport. For each route the used shipping systems are indicated. All shipping systems, including the ones used for air transport, have been properly qualified via thermal qualification, distribution testing and shipping route verification.

A media fill simulation has been executed which confirmed that the aseptic handling procedures and the environmental conditions for the filling step are considered appropriate for the production of FP. The operating parameters used for the media fill are set to challenge worst-case conditions that may occur during routine manufacturing and operational conditions. The vials are filled at high speeds (higher risk for interventions) and low speeds (prolonged exposure) to simulate worst-case production conditions. Filling is done immediately after sterile filtration. The sterile filtered bulk is not stored. Maximum times are indicated for each FP process step (all CPPs). Therefore, the maximum time for the complete FP process is defined as well as the maximum time of FP vials exposed to 2-8°C and to 25°C.

Vials are depyrogenated and caps are steam sterilised. The depyrogenation and autoclave have been adequately validated. The rubber stoppers are provided by the supplier as ready-to-use sterile rubber stoppers. The applicant has provided the requested information on the sterilisation of the stoppers. The stoppers are deemed acceptable for use in the FP container. Appropriate filter validation reports are provided and it is concluded that the filters are deemed suitable for the intended use.

For the second FP site, sections 3.2.P.3.5 Process Validation and/or Evaluation – Depyrogenation of Glass Vials, 3.2.P.3.5 Process Validation and/or Evaluation – Sterilisation of Equipment Components and Stoppers, and 3.2.P.3.5 Process Validation and/or Evaluation – Decontamination of Filling isolators should be provided post-authorisation (**recommendation 5**).

Filled FP at first site is then shipped (between -30°C and -15°C) to a packaging site, where labelling and secondary packaging proceeds. This site then ships the packaged product (between -30°C and -15°C)

to the Janssen Distribution Centres where it is stored between -30°C and -15°C. The shipping of the FP has been evaluated through a shipping route verification study and a distribution testing study which evaluated the impact of shipping on product packaging, including container closure integrity of the vials.

Product specification

Release and stability specifications as well as description of the analytical procedures were provided. The parameters tested are appearance (degree of coloration, clarity, and visible particles), identity by (ID)-PCR and virus protein fingerprinting by RP-HPLC, potency with transgene expression by quantitative ELISA and infectious units by QPA, quantity (virus particles) by VP-qCR, purity (aggregates average hydrodynamic radius and polydispersity) by DLS, safety tests (sterility, bacterial endotoxins, container closure integrity) and general tests (pH, osmolality, extractable volume, and polysorbate 80 concentration). The FP specification acceptance criteria have been sufficiently justified and the specification ranges are deemed acceptable.

The FP specification for infectious units is considered the most important parameter for FP. The initially proposed lower limits for FP infectious units at release and end-of-shelf-life (EOSL) were lower than the potency of the phase 3 clinical lots and could not be considered as clinically qualified/justified (this was a major objection). Subsequently, the applicant increased the infectious units release lower limit and the end of shelf life limit.

Since for immunogenicity and clinical efficacy the potency as expressed in infectious units is relevant, the potency of the vaccine should be expressed on the labelling in line with other viral vaccines. Therefore, it was proposed to change the labelling to "not less than 8.92 $\log_{10}$ Inf.U/dose", instead of "not less than 2.5×10^{10} VP/dose". The applicant agreed to express the labelling in Inf.U.

Identity, bacterial endotoxins, osmolality, extractable volume and polysorbate 80 concentration are not tested during stability studies. A test for replication-competent adenovirus (RCA) is performed on the AS only. The ratio infectious units/viral particles is established at AS level and a similar specification has also been established for FP release.

Since currently only limited experience is available for the polydispersity specification, the applicant's proposal to report the result without an acceptance criterion is acceptable. For the time being it is agreed that FP aggregates are sufficiently controlled by the hydrodynamic radius specification. However, it is expected that an acceptance criterion for polydispersity will be established and justified once sufficient experience and data for this parameter are available (**recommendation 12**).

For the transgene expression a qualitative ELISA is performed to confirm expression. The applicant has properly justified the use of the assay for determining the transgene expression. The validation of this method has been briefly described. In addition, the applicant has pointed out how the relative transgene expression levels correlate linearly with infectivity results obtained by QPA, the latter being a quantitative way to measure infectivity of Ad26.COV2.S.

For the extractable volume, the applicant states that the acceptance limit of ≥2.5 mL ensures that enough volume can be extracted from the vial for correct dosing of up to five doses of 0.5 mL each (tested as 5 times an extraction of 0.5 mL).

Due to the implementation of ICH Q3D guideline on elemental impurities, compliance to ICH Q3D should be confirmed. Although vaccines are strictly taken, not within the scope of ICH Q3D, a risk assessment of the elemental impurity level in the finished product should be performed in order to keep the same level of safety assurance on elemental impurities, as requested according to Ph. Eur. general chapter 5.20. A summary of this risk assessment and a control strategy for elemental impurities in accordance with ICH Q3D should be provided (**recommendation 13**).

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

No new impurities are introduced during the FP manufacture. The major objection is considered resolved.

Analytical methods

Descriptions were provided for all the analytical methods used for FP release testing. The analytical methods for virus identity, protein fingerprinting, transgene expression, infectious units, virus particles and PS80 content are the same methods as used for the AS. Compendial methods are used for pH, osmolality, extractable volume, sterility, endotoxin, container closure integrity and appearance. The only FP-specific method is the assay for aggregates. All non-compendial methods were appropriately validated at each test site. Compendial methods were verified to demonstrate that the methods are suitable for use with the current product and that no interference/inhibition occurs. Method suitability and absence of interference by the product were demonstrated for the endotoxin and sterility tests.

Batch analysis

Batch analysis results are presented for clinical single dose finished product (FP) batches, non-clinical multidose FP batch, multidose commercial PPQ FP batches from the first commercial site and multidose commercial PPQ FP batches from the second site. Information regarding batch scale, manufacturing dates and genealogy is provided Also, additional characterisation test results are provided. The single-dose and multi-dose processes are highly similar. The main difference between the phase 3 process and commercial process is the scale of filling and the fill volume (single dose versus five-dose). The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The applicant provided a detailed description of the reference materials used during development. Reference material (RM) is used as a control in release, stability and in-process testing, and for characterisation methods throughout the product development lifecycle. The same reference material is used for AS and FP testing. RM includes research material (ResMat) and development reference material (DRM).

In the future, a primary reference material (PRM) and working reference material (WRM) will be derived from representative batches and qualified. The PRM and first WRM will be taken from different FP batches manufactured using the clinical Phase 3 DP manufacturing process. The FP used to prepare the PRM was made from AS from the small scale process (manufacturing process variant S-VAL-4) at 1 x 10^{11} VP/mL, and the FP used to prepare the WRM will be made from AS from the large scale process (manufacturing process variant S-VLF-2) at 2 x 10^{11} VP/mL. A qualification protocol for the primary reference material and working reference material has been provided and is deemed acceptable. For the time being, the DRM2 and DRM3 (both used during phase 3 studies) are considered sufficiently qualified and therefore suitable for use as reference material for commercial AS and FP.

The ResMat was used for testing clinical batches (Phase 1, 2, and 3) and as the RM to qualify RM Batch (DRM1). This lot is used in part of the Phase 3 trials until implementation of RM Batches (DRM2) and

(DRM3). The latter two are used for Phase 3 trials and first commercial lots (until a primary and working standard will be established in the future).

The applicant has provided a testing protocol for future primary reference standard and working reference standards, which is deemed sufficient and acceptable.

Stability of the product

The proposed shelf life of the Ad26.COV2.S FP is 2 years when FP is stored frozen at -25°C to -15°C, with a single storage period of 3 months at 2°C to 8°C (not exceeding the expiry date).

Within these 24 months, a 3 months storage at 2-8°C is also proposed. The FP should not be refrozen after it has been placed in storage at 2-8°C. The FP must be stored in the original packaging in order to protect it from light.

Only a few early time points of Ad26.COV2.S stability studies on clinical batches (Phase 1-3) are currently available. The shelf life is based on platform data from similar Ad26 products. These platform products were stored in the same vials as Ad26.COV2.S The same stability-indicating assays were used in the studies as are being used for Ad26.COV2.S commercial product studies. Up to 36 month-data are provided from more than 50 FP lots at different temperatures (-80°, -20°C). This includes data from 4 lots stored at -20°C for 36 months. These are considered sufficiently representative since the particles are identical (apart from the genome which contains a different insert).

Based on these data and input from other development studies, a conservative shelf life model was constructed to justify the proposed initial shelf life for Ad26.COV2.S FP. In this model, the following factors were taken into account: AS stability, shelf life specifications, expected losses during packaging and labelling, temperature excursions, in-use and an estimate of the average degradation slope.

Storage at -20°C or lower does not have any impact on FP quality; no trends are observed for potency. When stored at 2-8°C, a slight decrease in potency occurs over time. Using platform data and a model for potency decrease, the applicant has proposed that *'once removed from the freezer, the unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for a single period of up to 3 months, not exceeding the printed expiry date. Once thawed, the vaccine should not be re-frozen'*. This period is considered conservative when taking into account the statistical model and the stability data from other Ad26 products.

The applicant also indicates that the FP must be stored in the original packaging in order to protect it from light. As requested, the applicant provided information on the stability study and the risk assessment (in absence of photostability data). This is considered acceptable at this point. However, to evaluate the sensitivity of Ad26.COV2.S Finished Product when exposed to light stress, a study based on the ICH Q1B requirement should be performed. The samples should be tested for potency, turbidity, radius and aggregation (**recommendation 8**).

The clinical single dose FP batches and the commercial multidose FP batch included in the stability studies will be stored in accordance with applicable ICH guidelines. In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to EMA.

As regards the in-use shelf life of the FP, it was shown during product development that:

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

'Chemical and physical in-use stability of the vaccine has been demonstrated for 6 hours at 2°C to 25°C. From a microbiological point of view, the product should preferably be used immediately after first puncture of the vial; however, the product can be stored between 2°C-8°C for a maximum of 6 hours or remain at room temperature (maximally 25°C) up to 3 hours after first puncture of the vial. Beyond these times, in-use storage is the responsibility of the user.'

The applicant is requested to provide the stability data from PPQ FP lots from the facility when available. In addition, for each additional FP manufacturing site, FP stability studies should be initiated and these data can be provided post-approval (**recommendation 14**).

In addition, the applicant has investigated the possible impact of mechanical stress (experienced during transport) on the thawed finished product (potency and quality). No impact was observed. Moreover, it was also shown that the vaccine is relatively stable when exposed to room temperature for a limited period of time. Therefore, the applicant has included guidance in the SmPC with regard to possible temperature excursions above 8°C and transport of the thawed vaccine.

In conclusion, the FP shelf-life is adequately supported by the submitted data. A 2-year shelf life for the vaccine when stored between -25°C and -15°C (long-term storage) and the additional storage conditions described in section 6.4 (Special precautions for storage) of the SmPC are accepted.

Post approval change management protocol(s)

The applicant has provided a protocol for addition and validation of new sites for AS and FP production at a larger scale. Initially, batches for clinical development and small-scale commercial supply are manufactured at a bioreactor scale of small scale. A process scale-up was established to manufacture AS at large scale. New sites are foreseen to manufacture at the large scale. Compared to the process used for clinical and small-scale commercial manufacturing, the scale-up is mostly linear and the unit operations remain the same. Where applicable, prior knowledge from other AdVac/PER.C6 platform-based products has been and will be considered for the process design.

Process validation protocols are provided. In order to evaluate that each newly introduced AS manufacturing site is capable of consistently performing manufacturing process, a process validation/process performance qualification (PV/PPQ) campaign based on preliminary CPP and preliminary critical material attributes (CMA) will be completed. A minimum of 3 AS or FP lots will be produced for PPQ; acceptance criteria for CPPs and critical material attributes must be met (with potential necessary adjustments due to site or scale elements); results for IPC and release tests must comply with the acceptance criteria and the specifications.

The AS process at large bioreactor scale will be transferred to additional manufacturing sites. Implementation of new manufacturing sites may result in limited changes to process parameter set-points/ranges, equipment and raw materials. The applicant has previously successfully applied similar process changes, e.g., AS manufacturing site transfers, to manufacture other AdVac/PER.C6 platform-based vaccine candidates that have met their specifications. Initial release and characterisation testing of the large scale AS batches of other AdVac/PER.C6 platform-based vaccine products demonstrated comparable quality of the vaccine.

Initially, FP batches were manufactured for commercial supply. The commercial FP manufacturing process has been scaled up and will be transferred to additional sites to increase manufacturing capacity. To demonstrate comparability of AS or FP, a 2-tiered approach is proposed by the applicant. Initial comparability assessment (tier 1) will consist of comparison of release and IPC results and some limited characterisation. If the release results of both pre- and post-change FP batches are within the commercial specifications, it will be concluded that the initial comparability criteria are met and post-use lots will be

released for commercial use. This enables timely use of post-change materials to alleviate the high demand due to the COVID-19 pandemic. The additional characterisation test results (tier 2) will be provided post-approval. Given the COVID-19 pandemic and the current circumstances and urgency, this approach is deemed acceptable.

In addition, the applicant also proposes a post-approval change management protocol (PACMP) to optimise the cell culture steps and to use new equipment for stage 7 (chromatography) and stage 8 (diafiltration) to increase the AS process capacity. Process validation protocols and stability protocols are provided and a similar comparability analysis with two tiers is proposed.

The proposed PACMPs to introduce and validate additional AS production sites and FP production sites using processes at a larger scale, as well as to optimise the large scale AS process to increase capacity, and to demonstrate comparability of AS/FP, are deemed acceptable.

Finally, an additional PACMP has been proposed to add new QC testing sites. New QC sites will be qualified based on predefined analytical method validation or verification protocols. Compendial test methods will be verified at the new QC test site according to pharmacopeial requirements. Non-compendial test methods will be transferred by co-validation or by comparative testing (i.e., equivalency). Acceptance criteria for test method validation will be at least equally strict as the acceptance criteria used during original method validation as described in the dossier. The applied acceptance criteria are deemed sufficiently stringent and thus adequate. This PACMP and the proposed approach to introduce and qualify additional QC testing sites is deemed acceptable.

Adventitious agents

The applicant adequately described the adventitious agents' safety aspects.

Adventitious agents' safety for Ad26.COV2.S is assured through the design and control of the manufacturing process: controlled selection and appropriate specifications for raw materials and excipients, and specifications, in-process controls and release testing for starting materials, AS and FP.

None of the raw materials used in the manufacture of the MVS, intermediate virus passage, WVS, inoculum, MCB, WCB, LVHD, AS, or FP batches was identified as being of direct animal or human origin. None of the excipients was of animal or human origin. However, one of the raw materials used in the manufacture of the MVS/WVS/AS (as a processing aid) was identified as involving animal-derived products in its production process: benzonase. It is demonstrated, though, that it does not present any adventitious agents safety risk. No transmissible spongiform encephalopathies (TSE) risk deriving from the use of these materials has been identified.

With respect to microbial adventitious contamination (bacteria, fungi, mycobacteria, and mycoplasma), appropriate microbial controls are performed on the starting materials. Furthermore, all the solutions and buffers used in the downstream process are manufactured aseptically according to cGMP referential conditions by a validated sterile filtration method and tested according to the European Pharmacopoeia. In addition, microbial controls are performed during the cGMP manufacturing. Adequate controls and specifications for starting materials, raw materials and excipients, appropriate specifications, in-process controls, release tests, and validation of the relevant steps demonstrate that the MVS, WVS, AS and FP are prepared under conditions designed to minimise the risk of microbial contamination.

With respect to adventitious viruses, the preMVS material has been tested for in vitro adventitious agents (on Vero, MRC-5, and HeLa cells); no viral contaminants were detected. Testing of the MVS with respect to viral safety is detailed. No viral contaminants were detected. The PER.C6 TetR-derived cell substrates have also been tested extensively tested by the general viral safety tests for adventitious or endogenous viruses/retroviruses and by PCR for specific human viruses. No porcine or bovine viruses were detected.

The manufacturing process does not have a dedicated, validated viral clearance step. Because the product is a non-enveloped virus vector, it is not possible to implement specific (non-enveloped) viral clearance steps in the manufacturing process.

The applicant has included RCA test as release test for the AS. TSE, viral and microbial safety has been suitably assured.

GMO

Refer to the ERA assessment report and section 2.3.5.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The quality information for the COVID-19 Vaccine Janssen presented during the MAA has been thoroughly assessed. A list of questions was generated, which included three major objections, related to GMP, nitrosamine risk assessment and acceptance criterion for infectivity during shelf-life.

Adequate responses were provided to address the major objections and other concerns and to support Conditional Marketing Authorisation. Additional validation, release and comparability data have been submitted for AS and FP manufacturing sites. Necessary EU GMP certificates for the manufacturing and testing sites were subsequently provided.

Further information is provided below on the resolution of the major objections and the rationale for accepting some open issues to be addressed as a specific obligation post-marketing. Several other issues are further highlighted as recommendations to be addressed by the applicant post-approval.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

The dossier is of acceptable quality however, certain information and data remain to be provided. Despite the short time frame of product development, sufficient data to support conditional marketing authorisation are provided and key areas requiring completion are explained below. These further data will be addressed in a specific obligation and other post-approval measures (recommendations).

The Ad26.COV2.S AS and FP manufacturing processes and process controls are described in detail. Quality of process intermediates is adequately controlled by in-process controls. Both a small-scale AS process and a large scale AS process are included in the MAA.

The following issues have been addressed during the procedure:

A major objection was raised with regards to the GMP compliance of AS and FP manufacturing sites. Proof of GMP compliance has been provided for all relevant sites. In addition, GMP inspections have been performed for and GMP certificates have been issued resolving the major objection.

The small scale AS process at Janssen Vaccines and Prevention B.V. (Leiden, NL) and the large scale AS processes at Janssen Biologics B.V. (Leiden, NL) and Emergent Baltimore (USA) have been properly validated. In addition, production of the inoculum (used for the large scale process) has been validated and results from the 3rd PPQ lot should be provided post-approval (**recommendation 1**).

The FP manufacturing process at the first commercial FP site is adequately validated. Some additional characterisation data to confirm homogeneity and the hold times should be provided post-approval (**recommendation 7**).

With regards to the second commercial FP site, batch data of the 3 PPQ lots were provided. All results were compliant with the FP specifications and also highly similar to release test results from phase 3 clinical lots and batches from the first commercial site. This is sufficient to support approval of the conditional marketing authorisation, in the context of the COVID-19 pandemic public health emergency, supporting a conclusion that the site can consistently manufacture FP. However, full PPQ data (including hold time) are required for the second commercial site to complete the data package from this facility. These data are requested post-approval (**specific obligation 1**).

Data supporting proven acceptable ranges (PAR) for CPP and non-CPP (nCPP) are provided. However, some parameters are still being evaluated and are classified as potentially critical. A final conclusion on the criticality of these parameters should be provided upon availability (**recommendation 10**). 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 optimisations were introduced for the AS/FP processes that will be used for the initial commercial batches. To demonstrate comparability, the applicant has used a 2-tiered comparability approach that comprises a combination of release testing and additional characterisation testing. Both the results for release tests and characterisation tests were highly similar. Therefore, it can be concluded that the AS lots from the commercial small scale process at Janssen Vaccines & Prevention B.V. (Leiden, NL) are comparable to the lots used in the Phase 3 clinical trials. Moreover, it was also shown that AS lots produced using the large scale processes at Janssen Biologics B.V. (Leiden, NL) and Emergent Baltimore (USA) were comparable to clinical AS lots and to AS lots small scale site. Tier 2 comparability data to confirm that the large scale AS (from Janssen Biologics B.V., Leiden, NL) is comparable to the small scale process material (from Janssen Vaccines & Prevention B.V., Leiden, NL) (**recommendation 2**) and tier 2 comparability data to confirm that the large scale AS (from Emergent, USA) is comparable to the AS from the other commercial AS sites (**recommendation 3**) should be submitted post-authorisation.

With regards to the FP manufacture, FP lots from the first FP site were shown to be comparable to the phase 3 clinical FP lots. Tier 2 comparability data for confirmation should be submitted post-authorisation (**recommendations 6**). In addition, a forced degradation study (thermal stress) is ongoing to support further comparability assessment between clinical Phase1/2 lots and phase 3 lots (**recommendation 9).**

With regards to the second site, the batch release data (3 lots) are very consistent and also highly similar to release data from Phase 3 clinical lots and batches from the first commercial FP site and provide already some indication about the process validation and comparability. However, comparability data (tier 1 and tier 2) are requested to confirm that the FP from the second commercial site is comparable to the FP from the first site and consequentially also confirm comparability with clinical material (**specific obligation 1**). This approach is acceptable in the context of the COVID-19 pandemic public health emergency.

FP release testing for endotoxin and sterility will be temporary performed in registered sites that are located in the US until 30 June 2021. From 30 June 2021 onwards, FP release testing for endotoxin and sterility will be performed by a site located in the EU. This is deemed acceptable in the context of the COVID-19 pandemic public health emergency. As it concerns compendial tests (endotoxin and sterility), suitability testing will be performed according to pharmacopoeial requirements for method transfer qualification. **Annex II.A** of the Product Information reflects this temporary exemption.

The absence of evaluation of the risk of the presence of nitrosamine impurities in the finished product in accordance with the published Art. 5(3) Referral on Nitrosamines was raised as a major objection. The

applicant has performed a risk assessment for both the AS and FP Manufacturing process with regard to possible nitrosamine impurities. Importantly, it concerns a biological process that does not contain any chemical synthesis steps. No nitrosating agent is used in the manufacturing process. Based on the AS/FP manufacturing process conditions and the nature of the starting materials, raw materials, excipients and equipment used, the risk for nitrosamines is considered negligible.

A summary of this risk assessment of the elemental impurity level in the finished product in accordance with ICH Q3D should be provided post-approval (**recommendation 13**).

A third major objection was raised on the need to revise the lower limit of the FP specification for infectious units. To address this issue the applicant has increased the infectious units release lower limit and the end of shelf life limit. In addition, the test for RCA has been included in the AS specifications. The upper limit for HCP (AS specification) has been revised. The specifications proposed for the AS and FP are deemed acceptable. However, it is expected that an acceptance criterion for polydispersity will be established and justified once sufficient experience and data for this parameter are available (**recommendation 12**).

Since for immunogenicity and clinical efficacy the potency as expressed in infectious units is relevant, the potency of the vaccine should be expressed on the labelling in line with other viral vaccines. Hence, it was proposed to change labelling to "not less than 8.92 $\log_{10}$ Inf.U/dose", instead of "not less than 2.5×10^{10} VP/dose". The applicant agreed to express the labelling in Inf.U.

Container closure systems of AS and FP were properly qualified. The applicant should provide the results of the 6 month time point of the FP container leachables (**recommendation 11**).

A shelf life of AS when the AS is stored frozen was proposed by the applicant.

The proposed shelf life for the FP 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. These shelf lives are based on platform data from similar Ad26 products. The currently proposed shelf lives for AS and FP are deemed sufficiently qualified and justified and are thus acceptable. Product-specific stability data will be generated and should be provided when available (**recommendations 4** and **14**). The proposed stability testing protocols are acceptable. Additionally, the applicant should provide data from photostability studies post-approval (**recommendation 8**).

The applicant has provided PACMP protocols for addition and validation of new sites for AS and FP production at a larger scale. Process validation protocols include production of a minimum of 3 AS or FP lots for PPQ; acceptance criteria for CPPs and critical material attributes must be met; results for IPC and release tests must comply with the acceptance criteria and the specifications. To demonstrate comparability of AS or FP, a 2-tiered approach is proposed. Initial comparability assessment (tier 1) will consist of comparison of release and IPC results and some limited characterisation. If the release results of both pre- and post-change FP batches are within the commercial specifications, it will be concluded that the initial comparability criteria are met and post-use lots will be released for commercial use. This enables timely use of post-change materials to alleviate the high demand due to the COVID-19 pandemic. The additional characterisation test results (tier 2) will be provided post-approval. Given the COVID-19 pandemic and the current circumstances and urgency, this approach is deemed acceptable. Furthermore, another PACMP has been provided to optimise the cell culture steps and to use new equipment for stage 7 (chromatography) and stage 8 (diafiltration) to increase the AS process capacity. Process validation protocols and stability protocols are provided and a similar comparability analysis with two tiers is proposed. The PACMPs and the proposed approach to introduce and validate additional AS production sites and FP production sites using processes at a larger scale, as well as to optimise the large scale AS process to increase capacity, and to demonstrate comparability of AS/FP, is deemed acceptable.

Finally, an additional PACMP has been proposed to add new QC testing sites. New QC sites will be qualified based on predefined analytical method validation or verification protocols. Acceptance criteria for test method validation will be at least equally strict as the acceptance criteria used during original method validation as described in the dossier. This PACMP and the proposed approach to introduce and qualify additional QC testing sites is deemed acceptable.

All other issues raised during the procedure are considered solved and from quality point of view the marketing authorisation application for COVID-19 vaccine Janssen is acceptable.

Impact on the benefit-risk assessment

Efficacy, safety and immunogenicity was demonstrated using clinical batches of the vaccine.

The active substance and finished product are acceptable in relation to control of critical quality attributes and impurities.

Studies to demonstrate batch-to-batch consistency of the finished product in terms of process validation studies/process performance qualification studies (PPQ) have not been fully completed in the finished product commercial manufacturing sites. Nonetheless, sufficient data have been provided for full scale lots (including some PPQ lots) at the commercial sites and at other sites using the commercial process.

In order to confirm the consistency of the finished product manufacturing process, the applicant is requested to provide the completed process validation (including hold times) and comparability data for the Catalent Indiana LLC site.

It is considered likely that the applicant will be able to provide the requested data and thereby fulfil the specific obligation.

Based upon the applicant's justification and commitment, and in view of the public health emergency, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment in order to complete the proposed specific obligation. Based on the applicant's plans and documentation, it is expected that data to fulfil the quality SO will be submitted by mid-August 2021.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The data presented to support consistent quality of this medicinal product is considered sufficient in the context of a conditional marketing authorisation in the current (COVID-19) pandemic emergency situation. To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant is requested to fulfil the specific obligation (SO) post-approval.

The CHMP has identified a specific obligation to address the quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore is needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligation are mentioned below.

In accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods (see the proposed recommendations).

To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant should fulfil the following specific obligation (SOs) post-approval.

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

a. The applicant should provide the complete process validation/ process performance qualification (PPQ) data (including hold times) for US site. Information demonstrating proper validation of the proven acceptance ranges for the critical process parameters during PPQ should be provided. In addition, comparability data should be provided to confirm that the finished product (FP) from the second FP site is comparable to the FP from the first site. **One interim report with initial PPQ data and tier 1 comparability should be submitted by 31 March 2021, and a final report with all remaining PPQ results and tier 2 data should be submitted by 15 August 2021.**

In addition, since the analytical method transfer from the US to EU is ongoing, Annex II of the opinion will include:

> *'In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 30 June 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 30 June 2021 at the latest, in line with the agreed plan for this transfer of testing.'*

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Active substance

1) The applicant should provide the validation data of the third process validation inoculum batch produced at Janssen Biologics B.V. (Leiden, NL) by Q4-2021.
2) The applicant should provide the tier 2 comparability data to confirm that the large scale AS (from Janssen Biologics B.V., Leiden, NL) is comparable to the small scale process material by 30 June 2021.
3) The applicant should provide the tier 2 comparability data to confirm that the large scale AS (from Emergent, USA) is comparable to the AS from the other commercial AS sites by 31 July 2021.
4) The applicant should initiate stability studies (including at least 3 representative lots) for the large scale AS process at Emergent (USA). In addition, for each new AS manufacturing site, AS stability studies should be initiated. The applicant is requested to provide the AS stability data for 3 representative AS batches for each manufacturing scale (small scale at the Janssen Vaccine and Prevention B.V. site (Leiden, NL) and large scale batches produced at the Janssen Biologics B.V. (Leiden, NL)) when the respective studies have been finalised and the results are available (by Q2-2024).

Finished product

5) The applicant should provide the following updated sections for second FP site: 3.2.P.3.5 Process Validation and/or Evaluation – Depyrogenation of Glass Vials, 3.2.P.3.5 Process Validation and/or

Evaluation – Sterilisation of Equipment Components and Stoppers, and 3.2.P.3.5 Process Validation and/or Evaluation – Decontamination of Filling isolators by 31 March 2021.

6) The applicant should provide the tier 2 comparability data to confirm that FP from the first site can be considered comparable to the Phase 3 clinical FP lots by 30 June 2021.

7) Regarding the process validation of the first site, the applicant should provide the results from bulk homogeneity verification during formulation and sterile filtration and filling by 31 July 2021. In addition, the additional characterisation data to confirm the hold times should be provided by 31 July 2021.

8) To evaluate the sensitivity of Ad26.COV2.S FP when exposed to light stress, a study based on the ICH Q1B requirement should be performed. The samples should be tested for potency, turbidity, radius and aggregation by 30 September 2021.

9) The applicant should provide an updated section 3.2.P.2.3 Manufacturing Process Development – Comparability, including results from forced degradation studies using thermal stress conditions (which were performed as part of the comparability analysis between clinical Phase1/2 lots and phase 3 lots) by 30 June 2021.

10) A final conclusion on the criticality of the potentially critical parameters in an updated version of section 3.2.P.2.3 Manufacturing Process Development – Control Strategy Development – Critical Process Parameters should be provided. In addition, the applicant should provide an updated table 1 Summary of Critical Process Parameters and Associated PAR in FP Manufacturing Process in 3.2.P.2.3 Manufacturing Process Development – Control Strategy Development – Critical Process Parameters by 31 July 2021.

11) The applicant should provide the results of the 6 month time point of the FP container leachables study by 31 December 2021.

12) Regarding the FP specification for polydispersity, the applicant is requested to establish and justify acceptance criteria once sufficient experience and data for this parameter are available, by 31 December 2021.

13) The applicant should provide a summary of the risk assessment of elemental impurities in the Ad26.COV2.S finished product to confirm compliance to ICH Q3D Guideline by 31 March 2021.

14) The applicant should provide the FP stability data for the 3 FP PPQ batches from the first commercial FP site when the stability studies have been finalised and the results are available (by Q2 2024). In addition, for each additional FP manufacturing site, FP stability studies should be initiated.

2.3. Non-clinical aspects

2.3.1. Introduction

The proposed candidate vaccine is an Ad26 vector with deletions in the early region (E1) of the Ad26 genome, rendering it replication incompetent. The Ad26.COV2.S vector contains a transgene in the ΔE1A/E1B region which encodes a modified full-length SARS-CoV-2 spike (S) protein with stabilizing modifications, i.e. 2 amino acid changes in the S1/S2 junction that knock out the furin cleavage site, and 2 proline substitutions in the hinge region known to stabilise the prefusion conformation. The wild-type full-length S gene information was obtained from a SARS-CoV-2 clinical isolate (Wuhan, 2019, whole genome sequence NC_045512).

A similar Adenovirus type 26 (Ad26) vector encoding the glycoprotein (GP) of the Ebola virus Zaire (ZEBOV) Mayinga strain has been approved in Europe through Centralised Procedure (Zabdeno, INN: Ebola vaccine rDNA, replication-incompetent; Procedure No. EMEA/H/C/005337/0000). The current application concerns a single dose regimen.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The non-clinical pharmacology of the Ad26.COV2.S candidate was evaluated in mice, rabbits, Syrian hamsters, and non-human primates (NHP) (rhesus monkey). Before selection of Ad26.COV2.S, different vaccine constructs with design elements previously shown to be successful for other coronavirus S protein-based vaccines were compared in in vitro and in vivo studies. The combination of the wild-type signal peptide, the furin cleavage site mutations, and the proline substitutions translated into superior immunogenicity in mice, Syrian hamsters, and non-human primates (NHP) (Bos et al., 2020; Mercado et al., 2020; van der Lubbe et al., 2021). The *in vivo* testing in NHP showed that the design of Ad26.COV2.S was optimal in inducing robust neutralising antibody responses as well as protection following SARS-CoV-2 challenge (Mercado et al., 2020).

Mice

The **murine** model was used to examine immunogenicity by assessing antibody and cellular immune responses after immunisation, including T helper cell (Th) polarisation of the immune response. The mice used were aged 10 to 12 weeks, which is considered to correspond to adult age in humans. In study 9346-20004, a dose level dependent induction of binding antibodies was observed at day 14 and 28 after vaccination. The stabilizing mutations present in Ad26.COV2.S compare favourably with binding antibody titers induced by a vaccine candidate coding for WT Spike protein, and this is confirmed in the virus neutralisation assay. Data from IFN-γ ELISpot and intracellular cytokine staining (ICS) assays show that T cell responses are induced, with a higher response in the CD8+ T cell compartment compared to the CD4+ compartment and indicate that IFN-γ is predominantly generated by CD8+ T cells.

The second study (9346-20007) was designed to determine the Th1/Th2 balance induced by a single dose of Ad26.COV2.S (1/5th of a human dose). Immunogenicity of Ad26.COV2.S was compared to recombinant adjuvanted S protein, known to induce a Th2 type immune response. Ad26.COV2.S was shown to induce the Th1 associated cytokine IFN-γ in ELISpot and multiplex ELISA assays, in contrast to alum adjuvanted Spike protein, 2 weeks post vaccination. The Th1 skewed immune response was demonstrated by a favourable ratio of IFN-γ to the Th2 associated cytokines IL-4, IL-5 and IL-10. In Balb/c mice, high IgG1 subclass with no IgG2a is associated with a Th2 response, whereas a balanced IgG2a/IgG1 ratio is indicative of a Th1-directed response. The ratio of anti-S protein antibody subclasses IgG2a and IgG1 was significantly higher for Ad26.COV2.S compared to alum adjuvanted Spike protein, with high IgG2a levels observed only after Ad26.COV2.S vaccination. These results confirm the induction of a favourable immune response in view of a potential for vaccine associated enhanced respiratory disease (VAERD).

NZW Rabbits

An immunogenicity study in rabbits [study TOX14369 (TV-TEC-175060)] shows that immunisation with a dose corresponding to 1/10th or a full human dose induces an immune response towards the antigen of the insert, which qualifies this species as relevant for the toxicological assessment. In addition, a

second dose of vaccine 56 days after the first immunisation triggers a booster in both the humoral and cellular responses.

Syrian hamsters

In the two hamster efficacy studies, the challenge dose was 10^2 $TCID_{50}$, which is lower than the dose reported in some publications (Sia et al, 2020, Tostanoski et al., 2020), but justified by results from Van der Lubbe et al. showing that a low dose challenge inoculum (10^2 $TCID_{50}$) induces a comparable viral load and disease compared with higher viral dose challenges. This dose was therefore selected to allow assessment of the occurrence of more severe disease in this model compared to NHPs and to evaluate the theoretical risk for VAERD. However, it actually conferred rather mild pneumonia without any clinical signs apart from body weight loss.

The aim of the first challenge study performed in the hamster [TKO 707 (TV-TEC-175626)] was to compare immunogenicity and protection of Ad26.COV2.S with other Ad26-based candidate SARS-CoV-2 vaccines, in a one- and two-dose schedule. Animals were challenged 4 weeks following immunisation and followed for 4 days after infection. This 4-day follow-up period is also justified by prior studies (Van der Lubbe et al.), showing that a 4-day follow up time after challenge is the most optimal time point to simultaneously evaluate lung tissue viral load and histopathology.

A single immunisation with $1/50^{th}$ or $1/5^{th}$ of a human dose of Ad26.COV2.S induces S protein binding antibodies as of Week 2 post-immunisation. A second dose increased binding antibody titers but levels returned to those observed before the second dose within 4 weeks. A single immunisation with Ad26.COV2.S induced SARS-CoV-2 neutralising antibodies, starting at Week 2 and increasing at Week 4. In contrast to binding antibody titers, a second dose led to significantly higher neutralising antibody titers throughout the study period (challenge followed 4 weeks post-immunisation).

Ad26.COV2.S given in a 1-dose or 2-dose regimen resulted in a lower lung viral load compared with the Ad26.Empty mock-immunised animals. That load was below the limit of detection for the majority of animals immunised with Ad26.COV2.S. This reduction in viral load was however less apparent in the upper respiratory tracts as the presence of infectious virus after challenge was also detected in vaccinated challenged animals independent of the 1- or 2-dose schedule.

The results of histopathological examination confirm the viral load results, i.e. a 2-dose regimen with Ad26.COV2.S induced a significant reduction in LRT histopathology scores and limited effects on URT histopathology scores after challenge. Due to a technical error only limited histopathology data are available for the 1-dose schedule hampering any conclusion on the potential benefits of a 2-dose. Finally, there were no signs of VAERD observed in animals dosed with Ad26.COV2.S compared with the control group for any of the parameters assessed.

Four days post inoculation, body weight loss was significantly reduced in animals vaccinated with a single dose of Ad26.COV2.S compared to controls, but this reduction was not evident in the 2-dose group, compared with controls.

Although the addition of a second dose 4 weeks after the first immunisation induces an increase in neutralising antibodies in the hamster model, a clear benefit in terms of weight loss reduction, viral loads or pathological scores could not be demonstrated in this model.

Both in terms of immune responses and protection from infection, Ad26.COV2.S compared favourably with the other vaccine candidates tested in this study.

The second hamster experiment [TKO 766 (study TV-TEC-176250)] was designed to determine the immunogenicity and efficacy of Ad26.COV2.S in a 1-dose regimen in Syrian hamsters at different doses of 10^7 ,10^8, 10^9 or 10^{10} vp Ad26.COV2.S, with the highest dose corresponding to $1/5^{th}$ of a human dose. The negative control groups received 10^{10} vp of an Ad26 vector not encoding any SARS-CoV-2

antigens. In this study lower dose levels of Ad26.COV2.S were included, with the aim of inducing suboptimal immune responses, allowing breakthrough viral replication in the lungs post inoculation with SARS-CoV-2. Under these conditions it can be investigated whether there is any increased risk for VAERD compared with a non-vaccinated control group. Viral load, body weight loss, and lung histopathology were measured after inoculation. In the present experiment as well, there were no illness signs, apart from body weight loss, which appears similar among all groups, only slightly reduced by vaccination.

A single immunisation with Ad26.COV2.S led to dose level-dependent induction of S protein binding and neutralising antibodies, a dose level-dependent reduction in median lung viral load after inoculation with SARS-CoV-2 and a dose level-dependent reduction in LRT histopathology scores. A dose of 10^8 vp (or below) Ad26.COV2.S resulted in a breakthrough SARS-CoV-2 infection as measured by the viral load in lung tissue. If breakthrough infection occurred, no increase of viral load was noted compared with the infection in the control group. There was no indication of increased lung pathology in the vaccinated animals even at lower doses and no presence of eosinophils were noted upon histopathological analyses, showing that the presence of low levels of neutralising antibodies elicited by sub-optimal Ad26.COV2.S vaccine doses do not aggravate lung disease in challenged Syrian hamsters compared to controls.

The conclusions appear similar to those for the previous experiment in hamsters, i.e. prior immunisation seems to protect animals mainly from a lower respiratory tract infection and it seems that the benefits of the vaccine in terms of upper respiratory tract protection are not clearly apparent, as measured by viral load (infective and viral RNA material), histopathological scores and immunohistochemistry.

The applicant also conducted a correlate of protection analysis showing that the binding and neutralisation titers inversely correlate to the viral loads and histopathology scores in the lower respiratory tract.

The results published by Tostanoski *et al*. confirm some of the findings from the 2 studies reviewed above, i.e.; a single administration of $1/50^{th}$ or $1/5^{th}$ of a human dose of the Ad26.COV2.S protects against severe disease and mortality in hamsters infected with a high dose of $5*10^5$ $TCID_{50}$. The vaccinated animals showed a minimal interstitial pneumonia whereas the controls displayed moderate to severe multifocal pneumonia characterised by consolidation affecting 30 to 60% of lung parenchyma. This publication also confirms that humoral immune responses correlate inversely with lung viral load after challenge. Unlike in those previous studies, in this model a correlation of the humoral response with upper respiratory tract viral load was also identified.

The efficacy of the vaccine in hamsters in terms of protection against body weight loss was not clear from the two previous studies in hamsters discussed above. In this paper however, it seems that prior immunisation protects against severe weight loss noted in the naïve challenged animals (-4% versus -19.9%). This 4% loss in vaccinated animals actually looks similar to that reported in the above studies. It appears that prior immunisation of hamsters does not prevent a slight weight loss but seems efficacious to prevent an increased weight loss when severe disease is induced.

The presence of the virus in the gastrointestinal tract was not assessed in either studies but are reported in Tostanoski *et al.* showing that prior immunisation with Ad26.COV2.S decreases the amount and time of detection of viral load in GI, spleen, liver and kidney compared to sham challenged animals.

Based on the data presented in hamster immunogenicity and challenge studies we can conclude that vaccination with one or two doses of Ad26COV2.S at 10^9 and 10^{10} vp 4 weeks prior to challenge protects the animals from mild to severe infection as noted by reduction of findings in the lower

respiratory tract (viral loads, histopathology and immunohistochemistry). The antibodies generated following vaccination with Ad26.COV2.S correlate with protection in the lower respiratory tract of hamsters. Their correlation with protection of upper respiratory tract is not clearly established.

Non-human primates

The NHP model assessed the immune response following one administration of the candidate vaccine and the protection following challenge. The high level of genetic homology between NHPs and humans, and their comparative immunology make NHPs a suitable model for studies of vaccine immunogenicity.

In study NHP 20-09, the NHPs were immunised IM with a single dose of 10^{11} vp Ad26.COV2.S (N=6) which corresponds to twice the human dose. A negative control group received saline only. The NHPs were inoculated with $1x10^5$ $TCID_{50}$ SARS-CoV-2 strain USA-WA1/2020, by the intranasal and intratracheal routes 6 weeks after immunisation. Although this study serves as non-clinical proof of concept, it appears that all animals remained healthy throughout the study and no clinical signs or changes on pulmonary radiographs or in inflammatory parameters or even significant differences in scores upon histopathological examination are reported. In addition, a rapid decrease in viral load in both URT and LRT shown in sham immunised animals was also reported. This may be due to the fact that macaques only recapitulate moderate COVID-19 disease, the young age (3-9 years) and healthy status of the animals and also given the low viral load used to inoculate the animals compared to published data. In conclusion, although the NHP challenge model is considered adequate to demonstrate immunogenicity, and viral clearance, it appears insufficient to demonstrate efficacy against the disease. It can be considered relevant for the modelling of asymptomatic or mild to moderate forms of disease in humans.

The immunogenicity results show that a single immunisation with Ad26.COV2.S induces antibodies against the S protein as well as neutralising antibodies. Regarding the cellular responses, they are considered as rather low and variable.

The main efficacy read-out in the NHP study noted was the reduction of viral load in the upper and lower respiratory tract (URT/LRT) in the vaccinated animals as measured by reverse transcription polymerase chain reaction (RT-PCR) detecting sub-genomic SARS-CoV-2 mRNA (sgRNA). This viral load was below the limit of detection (LOD) in the LRT in 6/6 NHP immunised with Ad26.COV2.S, and in nasal swab samples, viral load was below the LOD in 5/6 NHP. All control animals showed detectable lung and nasal swab viral load after challenge. Rectal and throat swabs were not collected to assess the presence of the virus, and Luminex and ICS were not performed on BALs. This is unfortunate as those results would have been important for the assessment of the candidate vaccine absence of ERD potential (particularly in the absence of clinical disease in the controls). The histopathology findings were very mild especially in females of both groups and no histopathologic evidence of VAERD was observed in the NHP study.

Some limited data were presented on the immune response 2 weeks post challenge (at week 8 post immunisation). These data showed that levels of neutralising antibodies post challenge seem to remain at a stable level while binding antibodies seem to increase after challenge. The cause for this discrepancy is unknown. Regarding the cellular immunity, ICS was performed 2 weeks post challenge but not analysed in favour of analysis of clinical ICS data. ELISpot results show a decrease 2 weeks after challenge, compared to the response observed before challenge (timepoint 4 weeks after immunisation; response in 5 out of 6 NHP). The applicant hypothesised that recruitment of specific T cells towards respiratory tracts could have reduced the systemic cellular responses but this explanation remains only theoretical.

NHP Study 20-14 [study TV-TEC-176763] is a dose level **titration** study with Ad26.COV2.S, applying dose levels of $1x10^{11}$ vp, $5x10^{10}$ vp, $1.125x10^{10}$ vp, and $2x10^9$ vp, administered as a single dose, to

further characterise the relationship between humoral and cellular immunogenicity and protective efficacy. A single immunisation with Ad26.COV2.S dose level-dependently induced protection from SARS-CoV-2 infection in LRT and URT. Protection rate in the LRT was 100% within the groups that received either $1x10^{11}$ vp or $5x10^{10}$ vp Ad26.CoV2.S and 80% within the groups immunised with either $1.125x10^{10}$vp or $2x10^{9}$ vp (N=5 per dose level). Protection rate in the URT was reduced at each dose level titration step, from 100% to 80%, 60% and 20%. Ad26.COV2.S dose-dependently induced neutralising (measured by psVNA) and binding (S or RBD ELISA) antibodies. T cell responses, measured by IFN-γ ELISpot, were also dose dependent but rather low and variable.

Since a higher number of breakthrough infections was observed in the nose compared to the lung, these data suggest that protection in the upper respiratory tract may require higher vaccine doses offering a higher level of systemic immune responses. This study confirms that Ad26.COV2.S protects from infection as demonstrated in study NHP 20-09. In addition, a dose response relationship was demonstrated for immune markers as well as viral load.

Vaccination of rhesus monkeys with Ad26.COV2.S at all dose levels followed by inoculation with SARS-CoV-2, was associated with considerably lower average lung pathology scores and the absence of virus-induced lung pathology, when compared to unvaccinated/sham-dosed challenged animals, demonstrating protection against viral challenge. It should be noted that the additional subgroup of control animals, with an age of 7-8y (=efficacy only group), had higher average scores compared to the initial control group (PBS-vaccinated, and at the age of 5y like the vaccine groups); 33.2 versus 24.87 respectively. This is in line with viral loads in the LRT. Within these groups, there was considerable variability in lung histopathology scores, but there were no obvious differences between males and females. Thus, in the control animals in general but especially in the age-matched control group pneumonia induced after challenge was very mild and without clinical signs.

In addition to the evidence of protection, vaccination with Ad26.COV2.S was not associated with an increase in the severity of lung findings (no increase in lung scores) even in animals having a breakthrough infection when compared to unvaccinated animals after challenge, indicating there was no histopathologic evidence of VAERD.

Data from 3 NHP studies (NHP 20-07, 20-09 and 20-14) were pooled for **correlate of protection analysis**. The design of those studies is similar: NHP were vaccinated with a single dose of Ad26-based SARS-CoV-2 vaccine candidates (10^{11} vp for study 20-07 and 20-09, dose titration range 10^{11}-2.10^{9} vp for study NHP 20-14), followed by challenge via intranasal and intratracheal route with same strain (USA-WA1/2020) at same dose (10^{5} $TCID_{50}$) at week 6 or 7. Ad26.COV2.S was not evaluated in study NHP 20-07 but 7 other Ad26 SARS-CoV-2 vaccine candidates were tested in comparable conditions. The same immunogenicity assays (2 pseudovirus neutralisation assays (Nexelis pseudoparticle based on modified VSV; and BIDMC with pseudotyped particles made from a modified lentivirus backbone), 2 binding antibody ELISAs (full length S in prefusion-stabilised conformation (Nexelis) and RBD (BIDMC)) and a T cell assay (IFN-γ ELISpot) were used for samples obtained in all three studies. Also, the same assay was used to determine viral load in BAL and nasal swabs (RT-qPCR of SARS-CoV-2 E gene subgenomic ribonucleic acid (sgRNA).

Two logistic regression analyses were made independently: one dataset consisted of all vaccine candidates combined (N=51) and a second dataset containing only the Ad26.COV2.S candidate (N=26).

Based on the data generated with the final vaccine candidate, derived from studies NHP 20-09 and 20-14, the dose dependent increases in humoral immune responses correlate with protection from infection, especially in the URT. Since dosing-down still offered protection from LRT infection, with only 2 vaccinated animals showing viral replication in the lungs (1 each in the two lowest dose groups), this comes with less precision of the logistic regression models for lung viral load. Correlation between tests

assessing neutralising and binding antibodies has been demonstrated, and correlation of those markers with viral load is confirmed when the latter is expressed as a continuous instead of a binary variable. Binding antibody titers appeared to have a higher discriminatory capacity than neutralising antibodies.

Neutralising antibody levels had the highest discriminatory capacity across all vaccine candidates combined from all studies. When comparing the overall analysis of all candidates to the analysis with the final candidate only, a correlation of T cell responses to protection was only shown in the latter. However, although a dose response relationship is indeed identified for the final vaccine candidate, it should be clear that the responses are not higher than those seen for other candidates in study NHP 20-07.

For the logistic regression analysis of all candidates, it should be noted that interpretation of those results is less straightforward, especially because the final candidate was not part of study 20-07, and it also builds on the assumption that the immune responses induced by the different candidates are qualitatively similar. For the logistic regression analysis of the final candidate only, as indicated above, precision of this logistic regression model is low for the lung as dose titration did not lead to the expected reduced LRT viral load. Both strategies are therefore considered complimentary, but these limitations may influence the weight that should be attributed to the outcome of the logistic regression analysis. However, the models have not been used to determine a threshold to apply to human data sets, which would probably require more robustness and further justification of the relevance of the animal model of infection, not disease. No unfounded claims have been made. The overall conclusion is supported: binding and neutralising antibody titers observed 4 weeks after immunisation with a single dose correlate with protection from infection in LRT and URT, when challenged in the short term.

A passive transfer experiment in this NHP model shows that convalescent plasma dose-dependently protects from infection, indicating that humoral response induced after infection is sufficient for protection (McMahan *et al*.). Ad26 vaccine-induced neutralising or binding antibodies could thus be mechanistically involved in protection but it remains to be determined if vaccine-induced humoral response is sufficient for protection or alternatively that antibodies could also act as surrogate of the actual protective effector mechanisms that may well be multifactorial.

Further evidence on the type of T cell response induced by vaccination was provided through a publication by Solforosi *et al*. (not peer reviewed). In this publication, a Th1 response was characterised by CD4+CD69+ T cells expressing IFN-γ and/or IL-2 and not IL-4, IL-5 and/or IL13 and a Th2 response was characterised by CD4+CD69+ T cells expressing IL-4, IL-5 and/or IL-13. Th1 skewing of the immune response is demonstrated in aged monkeys. Animals vaccinated with alum adjuvanted spike protein also induced comparable levels of antigen specific Th1 cells, but unlike the Ad26.COV2.S vaccine, activation of Th2 cells likely occurred. A similar intracellular cytokine staining was used for human samples from the phase I/IIa clinical trial, equally demonstrating Th1 skewing of the immune response (Sadoff *et al*. 2020). In addition, this publication describes that immune response and protection from challenge have been demonstrated in **aged** monkeys. These data support earlier studies, NHP 20-09 and NHP 20-14, with demonstration of protection in lower respiratory tract. It should be noted that in contrast to previous NHP studies, the G614 SARS-CoV-2 challenge strain was used. In study NHP 20-14 a dose response relationship was shown for protection from infection in upper respiratory tract. In the current study, only a partial protection of the URT was observed in the vaccinated animals. The applicant suggested that several factors may have contributed to this finding, like age of the animals, time of the challenge and the strain used. A detailed assessment, in absence of a study report, is not possible at this stage but increase in temperature and signs of interstitial pneumonia in aged monkeys from the unvaccinated control group indicate that older age is associated with a more severe disease compared to what was observed in control animals in previous studies in young adults.

Preliminary results of an ongoing **durability** challenge study in NHPs [study NHP 2020-3373 (TV-TEC-179493)] are publicly available (Roozendaal *et al*., not peer reviewed). The applicant analysed whether vaccination with Ad26.COV2.S provides protection in macaques 6 months after the first vaccination, and whether the degree of protection could have been anticipated based on the derived correlates of protection, as described above (Logistic regression models; based on data from studies NHP 20-07, 09 and 14). Groups of 7 macaques were vaccinated with either a one-dose ($5x10^{10}$ vp or $1x10^{11}$ vp) or two-dose regimen ($5x10^{10}$ vp/dose) of Ad26.COV2.S with either a 4-week or an 8-week interval between doses.

Although there is not much detail, the protection conferred by one or 2 immunisations seems to last for at least 6 months after the first immunisation, as shown by the antibody titers and the viral loads measured in the BALs. The presence of replicating virus was measured in the noses of vaccinated animals at similar levels than in controls, however animals receiving two administrations of the vaccine 8 weeks apart had significantly lower loads compared to the controls even though replicating virus is still measured as well in that group.

There is good agreement between the observed protection 6 months after vaccination with the predicted protection probability in the lung based on both pre-challenge binding and neutralising antibody levels and correlate of protection models. In the nose, the predicted levels were above those actually measured. Thus, the predictions for the probability of protection in the lower airways based on binding and neutralising antibody levels is more robust than that for the protection in the upper respiratory tract. These findings are considered supportive.

Secondary pharmacodynamic studies

No studies on the secondary pharmacodynamics have been performed, which is in accordance with applicable guidelines.

Safety pharmacology programme

Safety pharmacology studies have not been performed with Ad26.COV2.S, since data (e.g., detailed clinical observations) from repeat-dose toxicity studies with Ad26.COV2.S and other Ad26-based vaccines did not suggest that these vaccines have a significant impact on physiological functions (e.g., central nervous system, respiratory, and cardiovascular functions) other than those of the immune system. Therefore, and in line with the WHO guidelines on non-clinical evaluation of vaccines, stand-alone safety pharmacology studies are not deemed necessary.

Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions have been performed, which is in accordance with applicable guidelines.

2.3.3. Pharmacokinetics

Biodistribution studies were not performed with this specific COV2.S construct as formerly discussed and agreed during the scientific advices undertaken by the applicant.

The biodistribution profile of the Ad26 vector platform was evaluated in the rabbit using two Ad26-based vaccines encoding other antigens than the SARS-CoV-2 S protein.

In these biodistribution studies, one Ad26-based was administered at a dose of $5x10^{10}$ virus particles [vp], with animals sacrificed at Days 11, 61, or 91 following single IM injection, whereas for a second Ad26-based vaccine the animals received a dose of $1x10^{11}$ vp, with animals sacrificed on Days 11, 90, 120 or 180 following single IM injection of the vaccine.

Tissues from these animals were harvested for analysis of Ad26 vector DNA using a quantitative polymerase chain reaction (q-PCR) assay.

The results from both biodistribution studies show that the replication incompetent Ad26 vector does not widely distribute following IM administration in the animals. Vector DNA was primarily detected at the site of injection, draining lymph nodes and (to a lesser extent) the spleen. From these tissues, Ad26 DNA diminished slowly, with a small amount remaining in iliac lymph node of 1 animal at 180 days. In one of the studies, the vector DNA was below limit of detection in all other organs. Considering the removal of regions in the genome necessary for replication and the results of the two distribution studies performed with Ad26 platform, it is considered unlikely that the vector will replicate in human tissues. Notably, no biodistribution in gonads (ovaries and testes) was detected.

In addition, both Ad26-based vaccines tested in the biodistribution studies showed a similar pattern of (systemic) distribution and clearance when delivered via the IM route in the rabbit, despite carrying different transgene inserts. The Ad26 vector backbone used for Ad26.COV2.S is identical to the vector backbone of the Ad26-based vaccines that were tested in the available biodistribution studies. The only difference between the vectors, apart from the encoded antigen transgene, is the insertion of a tetracycline operon (TetO) motif in the cytomegalovirus (CMV) promoter sequence of the transgene expression cassette of Ad26.COV2.S. This is not considered to impact the biodistribution profile of the Ad26 vector.

2.3.4. Toxicology

The nonclinical safety profile of the Ad26.COV2.S vaccine has been assessed in two pivotal toxicology studies in New Zealand white (NZW) rabbits, a combined repeat-dose toxicity and local tolerance study, and a combined embryo-foetal and pre- and postnatal development (EF-PPND) toxicity study.

Table 2 Overview of Toxicology Studies in Support of the Development of the Ad26.COV2.S Vaccine

Test Species	Study Description	Vaccine, Route, Interval, and Dose Level	GLP	Study Report
NZW rabbit	Combined repeat-dose toxicity and local tolerance study	3 injections (Days 1, 15, 29; 2-week interval between doses), IM • Saline • $1x10^{11}$ vp	Yes	Mod4.2.3.2/ TOX14382
NZW rabbit	Combined embryo-fetal and pre- and postnatal development study	3 injections (Day 1[a], GD6 and GD20; 2-week interval between doses), IM • Saline[b] • $1x10^{11}$ vp[b]	Yes	Mod4.2.3.5.2/ TOX14389

[a] Day 1 = 7 days prior to pairing
[b] The study includes 2 subgroups: 1 group consisting of females that are necropsied on GD29 and have a uterine and fetal examination (external, visceral, and skeletal exams), and 1 group consisting of females that are allowed to give birth and in which the survival and development of the kits is evaluated through lactation day 28
GD: gestation day; GLP: Good Laboratory Practice; IM: intramuscular; NZW: New Zealand white; vp: virus particles

Repeat dose toxicity

A specific GLP-compliant repeat-dose toxicity and local tolerance study with Ad26.COV2.S (study TOX14382) was conducted in male and female NZW rabbits to evaluate its toxicity and to assess the potential reversibility, persistence or delayed occurrence of any findings 3 weeks after the last vaccination. The rabbits were injected IM with a control solution (0.9% sodium chloride) or 1×10^{11} vp Ad26.COV2.S on three occasions with a 14-day interval period (Days 1, 15 and 29). This dose and interval encompass the actual clinical dose and schedule, which is acceptable. The rabbit was also demonstrated to elicit an immune response to the antigen contained in the vector, which qualifies this species for the safety assessment of the present vaccine.

Ad26.COV2.S administered on three occasions every 2 weeks at $1x10^{11}$ vp/dose induced a transient inflammation consistent with an immunologic response to vaccination, i.e.: minimal hyperthermia and minimal body weight loss or lower body weight gain after injection, increases in plasma proteins (CRP, fibrinogen and globulins) and white blood cell counts (monocytes and lymphocytes).

Microscopic pathology findings showed increased lymphoid cellularity of germinal centers in popliteal and iliac lymph nodes and the spleen, also consistent with an immune response to the vaccine. Overall, the findings were considered non-adverse and were partially or completely reversible after a 3-week treatment-free period.

The local changes consisted of transient local injection site dermal reactions associated with minimal to slight and reversible inflammation and haemorrhage at the injection site.

In conclusion, the repeat dose toxicity and local tolerance study did not highlight any unexpected findings. Those were mild, transient and as expected from a local/general inflammatory reaction subsequent to vaccination.

Genotoxicity and carcinogenicity

No genotoxicity and carcinogenicity studies were carried out, in line with relevant guidelines. Studies evaluating genotoxicity and carcinogenicity are normally not required for viral vaccines. Since no adjuvants or novel excipients are used in this product, absence of those studies is considered acceptable.

As regard Ad26 vector and its integration ability in nature, wild type adenoviruses do not integrate their genomes into the host cell chromosomes. With a few exceptions they replicate as linear, extra-chromosomal DNA (episomic) elements in the nucleus. The guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors EMEA/273974/2005 indicates that adenoviruses have traditionally been regarded as non-integrating.

Reproduction Toxicity

A GLP-compliant EF-PPND toxicity study (study TOX14389) was conducted in female NZW rabbits that received Ad26.COV2.S intramuscularly on Day 1 (i.e., 7 days prior to mating), followed by two vaccinations during the gestation period (i.e. GD 6, and GD 20). The design of this study was discussed with CHMP and considered appropriate.

The rabbit is an acceptable model for developmental toxicity studies, and the dosing strategy ensures induction of a maternal immune response during mating and early gestation, evaluation of potential direct embryotoxic effects of the components of the vaccine formulation and the (direct) effects of the vaccine during late gestation, and a sustained maternal immune response up to lactation.

There were no adverse effects of treatment on survival, clinical observations, body weight, body weight change, food consumption, reproductive performance, fertility, ovarian and uterine examinations, parturition, or macroscopic evaluations in parental females.

No adverse effect of treatment was seen on foetal body weights, external, visceral, and skeletal evaluations on GD 29, or F1 kit evaluations from LD 0-28 (sex ratios, survival, body weights, clinical findings, developmental evaluations, and macroscopic evaluations).

The assay used for immunogenicity is a qualified SARS-CoV-2 spike ELISA. All immunised animals and their foetuses had high SARS-CoV-2.S protein-specific antibody titers, indicating that maternal antibodies were transferred to the foetuses. While antibody titers of foetuses were comparable to that in the does, titers in kits (measured on LD28) were 1.3-fold lower.

In conclusion, the reproductive and developmental toxicity study did not reveal any evidence of impaired female fertility and did not indicate harmful effects with respect to reproductive toxicity, while exposure of dams and offspring was confirmed by detection of antibody in ELISA.

Previous studies submitted with Ad26.ZEBOV vaccine in the rabbit did not highlight significant treatment related effects on reproduction or on F0 or F1 animals after administration 8 days prior to mating and at GD6.

Local Tolerance

No stand-alone local tolerance studies were submitted. This is acceptable and in line with relevant guidance on non-clinical vaccine development since local tolerance was evaluated in a repeated dose toxicity study.

2.3.5. Ecotoxicity/environmental risk assessment

Ad26.COVS.2 is a recombinant Adenovirus26 that has been rendered replication-incompetent by deletion of the E1 region of the wildtype Ad26. Ad26.COVS.2 is produced in an E1 complementing cell line, without any DNA sequence overlap between the Ad26.COV.S vector and the cell line, thereby precluding the formation of replication competent adenovirus (RCA). RCA testing of drug substance DS was conducted for several small- and large-scale processes and the results complied with the acceptance criteria specifications.

Both the non-replicative nature and the anticipated biodistribution profile upon intramuscular injection of Ad26COVS.2 is assumed to minimise co-infection events with wild-type adenoviruses, E1-complementing viruses or coronaviruses. An assessment of the effect and likelihood of recombination events concludes that resulting recombinants would either be non-replicative or will have no increased risk profile as compared to the circulating wild-type viruses that are present in the individual at the time of co-infection. While it is anticipated that exposure of unintended individuals to Ad26COVS.2 will be several orders of magnitude lower as compared to the dose administered for vaccination, results obtained with clinical trials completed so far indicate good tolerability and reveal no particular safety concerns distinct from other Ad26-based vaccines.

Risk management strategies

Even though the overall risk of Ad26.COVS.2 is deemed negligible, measures have been taken by the applicant to minimise the likelihood of spread in the environment or to non-target individuals.

The SmPC gives some guidance in relation to protection of personnel during handling and administration, including disinfection of accidental spills in section 6.6: "Potential spills should be

disinfected with agents with viricidal activity against adenovirus". Since the environmental risks of Ad26.COVS.2 are negligible, the inclusion of additional risk management strategies for reasons of environmental safety and safety of non-target individuals is not necessary.

The overall risk for human (non-vaccinated individuals) and the environment under the proposed conditions of release of Covid-19 Vaccine Janssen is negligible.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Ad26.COV2.S is an adenoviral vector that encodes a modified variant of the S protein that is stabilised in its prefusion conformation. This vaccine construct was shown to induce superior immunogenicity in mice, Syrian hamsters, and non-human primates and protection following SARS-CoV-2 challenge in NHPs and hamsters compared to other vaccine candidates explored by the applicant.

Immunogenicity of the Ad26.COV2.S vaccine was tested in mice, rabbits, Syrian hamsters, and NHP. The vaccine elicits a dose-dependent binding and neutralising antibody response in the species tested and additionally induces a cellular immune response in mice, rabbits, and NHP, which is rather low and variable. The applicant showed that the Ad26.COV2.S vaccine elicited a Th1 skewed immune response in mice and NHP.

The high level of genetic homology between NHP and humans, and their comparative immunology make NHP a suitable model for studies of vaccine immunogenicity and efficacy studies. The Syrian hamsters were selected as they are described as permissive to SARS-CoV-2 replication and display widespread lung pathology and clinical signs including weight loss. In contrast to the NHP model, shown to be an infection model but not suitable to demonstrate protection from disease, the hamster model shows more severe disease (Muñoz-Fontela, C. et al., 2020).

Challenge studies performed in NHPs have shown reduced viral load in the upper and lower respiratory tracts in vaccinated animals compared to controls. The NHP challenge model was considered adequate to demonstrate immunogenicity, and viral clearance, but appears insufficient to demonstrate efficacy against the disease. In a titration study in NHPs, a dose-dependent humoral immune response was demonstrated. While protection from infection in the lower respiratory tract was observed with little breakthrough cases even in the low dose groups, viral load in the upper respiratory tract was dose dependent. Preliminary results of an immunogenicity and efficacy study in aged NHP (VH808.681) have been provided through a manuscript (Solforosi *et al*.) and indicate that immune responses induced by Ad26.COV2.S vaccination confer protection in older animals. Finally, preliminary data from an ongoing durability study indicate that the immune response lasts for at least six months and confers protection to lower respiratory tract infection (Roozendaal *et al*.).

It seems that prior immunisation of NHPs confers protection more in the lower respiratory tracts compared to upper tracts 6 months after the first administration of the vaccine. Protection from upper respiratory tract infection was high shortly after vaccination of adult NHPs with high doses of Ad26.COV2.S (NHP 20-09). However, the titration study (NHP 20-14) with a dose level-dependent protection of URT suggested that protection in the upper respiratory tract may require higher vaccine doses offering a higher level of systemic immune response, compared to protection from LRT viral replication. Another study in older NHPs has also only shown partial protection of URT infection. In this new duration study, with only a small subsets of animals protected from URT viral replication, the applicant suggested that systemic binding and neutralising antibody levels likely are associated with a

distinct mechanistic correlate of protection in the nose early after vaccination, rather than being a mechanistic correlate of protection themselves.

The applicant complemented the non-clinical package with two humoral immunogenicity and challenge studies in a SARS-CoV-2 Syrian hamster challenge model. Ad26.COV2.S significantly reduced viral load in the lung and lower histopathological scores compared with mock vaccinated controls. However, the difference was less apparent in the upper respiratory tract where viral load and histopathological findings were not very different from unvaccinated animals. Like the experiments in the NHPs, the low challenge dose conferred rather mild pneumonia without any clinical signs in the unvaccinated control animals, apart from body weight loss in hamsters.

Data from a dose level titration study performed in hamsters showed dose level-dependent reduction of efficacy and partial breakthrough infection in the lower respiratory tract at lower dose levels. The protection of vaccination against weight loss was not really apparent in the 2 experiments reported here, however, some beneficial effects of Ad26.COV2.S on weight loss were noted in a study by Tostanoski *et al*. using a more stringent SARS-CoV-2 challenge dose, demonstrating significant protection when the body weight loss is severe.

It is additionally considered that the theoretical risk of SARS-CoV-2 vaccine-associated enhanced respiratory disease (VAERD) has been sufficiently addressed by the applicant. The structure of the Spike coded by the vector stabilised in its prefusion conformation, the Th1 skewing of the immune response confirmed in mice, NHPs and rabbits as well as the absence VAERD noted in the challenge studies based on assessments of lung histopathology and absence of signs of clinical disease contribute to conclude that this risk is low.

In both animal models, two different challenge strains were used, D614 which is related to the one expressed by the vaccine vector, and a G614 variant with higher infectivity. Protection from infection by emerging strains of interest will be addressed by assessing neutralising potential of clinical samples.

Finally, the applicant showed that in both Syrian hamsters and NHP, the binding and neutralising antibodies elicited by Ad26.COV2.S correlated with protection from infection with SARS-CoV-2 as measured by viral load in the respiratory tracts. Because immunogenicity and efficacy data are available from clinical studies, these non-clinical data are for the most part superseded and considered supportive of this application.

No assessment of a potential immune response toward the vector in itself was provided. Taking into account the available non-clinical and clinical platform data, as well as of clinical Ad26.COV2.S-specific data, the absence of non-clinical insert-specific vector immunity data is considered acceptable and sufficiently justified.

Pharmacokinetics

The biodistribution profile of the Ad26 vector platform was evaluated in the rabbit using two other Ad26 based vaccines. These platform biodistribution data are considered sufficient to inform on the biodistribution profile of Ad26.COV2.S, for which the same (replication incompetent) Ad26 vector backbone is used. This position has been confirmed and agreed in a previous Scientific Advice by EMA (EMA/CHMP/SAWP/369281/2020, dated 9 July 2020). It is further noted that the same platform biodistribution data were part of the MAA file for the Ebola vaccine component Ad26, Zabdeno (EU/1/20/1444/001).

The Ad26 vector shows a limited distribution profile following IM injection, with detection at the site of injection, draining lymph nodes and (to a lesser extent) the spleen. Clearance (reflected by a downward trend in number of positive tissues and vector copies over time, to levels close to, or below

the detection limit of the q-PCR methods used) of the Ad26 vector was observed, indicating that the vector does not replicate and/or persist in the tissues following IM injection.

Dissemination of Ad26 vector into breast milk or to/across the placenta has not been specifically assessed in these non-clinical biodistribution studies. Even if a small quantity was excreted via the milk, it would not be considered as a risk, since Ad26.COV2.S is a non-replicating vaccine and does not encode a complete virus.

Studies on absorption, metabolism and excretion were not performed, which is in accordance with the WHO Guidelines on the Nonclinical Evaluation of Vaccines.

Toxicology

The nonclinical safety profile of the Ad26.COV2.S vaccine has been assessed in two pivotal toxicology studies in New Zealand white (NZW) rabbits, a combined repeat-dose toxicity and local tolerance study, and a combined embryo-foetal and pre- and postnatal development (EF-PPND) toxicity study.

Overall, the repeat dose toxicity and local tolerance study did not highlight any unexpected findings. Those were mild, transient and as expected from local/general inflammatory reaction subsequent to vaccination. It also did not reveal any effects on male sex organs that would impair male fertility.

Female reproductive toxicity and fertility were assessed in a combined embryo-foetal and pre- and post-natal development study in the rabbit. In this study, a first vaccination of COVID-19 Vaccine Janssen was administered intramuscularly to female rabbits 7 days prior to mating, at a dose equivalent to 2-fold above the recommended human dose, followed by two vaccinations at the same dose during the gestation period (i.e., at gestational days 6 and 20).

This EF-PPND toxicity study did not reveal any vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. The parental females as well as their foetuses and offspring exhibited SARS-CoV-2 S protein-specific antibody titers, indicating that maternal antibodies were transferred to the foetuses during gestation. No COVID-19 Vaccine Janssen data are available on vaccine excretion in milk.

Dedicated male fertility studies are not routinely required for vaccines, and this is considered acceptable in this case as no concerns were raised in repeat dose toxicity study and biodistribution studies. Absence of juvenile animal studies is also acceptable since no target organs of toxicity have been identified.

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine are not expected to have genotoxic potential.

Overall, the toxicology studies were adequate and in accordance with the WHO guidelines on non-clinical evaluation of vaccines and scientific advice. 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.

2.3.7. Conclusion on the non-clinical aspects

No major non-clinical issues are identified in this application. A range of other concerns identified have been properly addressed by the applicant.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

2.4. Clinical aspects

2.4.1. Introduction

The trials performed by the applicant are still ongoing and all are randomised, placebo-controlled, and conducted in a double-blind fashion. The first-in-human VAC31518COV1001 is a Phase 1/2a to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 dose levels (5×10^{10} vp and 1×10^{11} vp). The data from this study supported the enrolment in the pivotal study VAC31518COV3001. A Phase 1 trial VAC31518COV1002 evaluates the safety and immunogenicity of Ad26.COV2.S. VAC31518COV2001 is a Phase 2a trial conducted in three EU countries to evaluate the safety and immunogenicity of the vaccine candidate. Two Phase 3 trials, VAC31518COV3001 and VAC31518COV3009, evaluate the efficacy, safety, and immunogenicity of Ad26.COV2.S in adults aged ≥18 years living in or going to locations with high risk for acquisition of Ad26.COV2.S infection.

This report presents the primary efficacy and safety analysis from study VAC31518COV3001, which was performed once the required 2-month median follow-up was reached (reached on 22 January 2021). In addition, interim immunogenicity and safety analyses from studies VAC31518COV2001, VAC31518COV1002 and VAC31518COV1001 are presented, as well as preliminary immunogenicity analysis for VAC31518COV3001.

GCP

The applicant claimed that the clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, EMA, in the context of the COVID-19 pandemic, gathered additional information on clinical trial conduct and GCP compliance of the studies included in this dossier, from the from EU and non-EU regulatory authorities and shared them with the CHMP to be considered in the assessment:

- Establishment Inspection Reports from GCP inspections performed by US-Food and Drug Administrations (USA Regulatory Authority) of five investigator sites in USA for study VAC31518COV3001 "A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older".
- Summary of the outcome from GCP inspection performed by the Peruvian Ministry of Health (INS) at one of the investigator sites located in Peru' for the study VAC31518COV3001.
- Summary of the outcome from GCP inspections performed by the Federal Agency for Medicines and Health Products of Belgium (FAMHP) at two of the investigator sites located in Belgium for the study VAC31518COV1001 "A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26COVS1 in Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older".
- Summary of the outcome from GCP inspections by the Health and Youth Care inspectorate of the Netherlands (IGJ) at two of the investigator sites located in the Netherlands for the study VAC31518COV2001 "A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels and Vaccination Intervals of Ad26.COV2.S in Healthy Adults

Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older and to Evaluate 2 Dose Levels of Ad26.COV2.S in Healthy Adolescents Aged 12 to 17 Years Inclusive".

Based on the review of clinical data, the above-mentioned reports and the general advisory input from the COVID-19 EMA pandemic Task Force (ETF), a request for GCP inspection of the clinical trials included in this dossier was not considered necessary by the CHMP.

- Tabular overview of clinical studies

The results described in this Clinical Overview are derived from 5 ongoing clinical studies which are being conducted in North America, Latin America, Europe, Africa, and Asia. An overview of ongoing and planned clinical studies with Ad26.COV2.S is provided in the following Table.

Table 3 : Overview of the studies included in the application

Study ID **EudraCT Number** **First Patient First Visit /** **Completion Date** **(day Month year)** **Study Status**[1]	**Country(ies):** **Number of Centers**	**Phase** **Study Description/Design,** **Study Population,** **Primary Objective(s)**	**Total Number of Subjects**	**Study Vaccine(s): Formulation (Route of Administration)** **Dose Regimen** **Duration of Treatment**	**Number of Subjects (by Vaccine Group)**
VAC31518COV1001 2020-001483-28 22 July 2020 Ongoing	BEL[3], USA: 12	Phase 1/2a Randomised, double-blind, placebo-controlled Healthy adults aged ≥18 to ≤55 years and adults aged ≥65 years. To assess the safety and reactogenicity of Ad26.COV2.S[1] at 2 dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM as a single dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	Planned: 1,045	Ad26.COV2.S: 1×10^{11} vp/mL; Placebo: 0.9% NaCl solution (IM injections) Cohorts 1a/b and 3: Days 1, 57: • Gp 1: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp • Gp 2: Ad26.COV2.S 5×10^{10} vp, placebo • Gp 3: Ad26.COV2.S 1×10^{11} vp, Ad26.COV2.S 1×10^{11} vp • Gp 4: Ad26.COV2.S 1×10^{11} vp,	Cohort 1a Gp 1: 77 Gp 2: 75 Gp 3: 75 Gp 4: 73 Gp 5: 77 Cohort 1b Gp 1: 5 Gp 2: 5 Gp 3: 5 Gp 4: 5 Gp 5: 5 Cohort 2a Planned: Gp 1: 30 Gp 2: 30

				placebo • Gp 5: placebo, placebo <u>Cohort 2a:</u> Ad26.COV2.S 5×10^{10} vp in a single-dose primary regimen (Day 1) with or without a single booster vaccination at 6, 12 or 24 months after completion of the primary regimen Placebo on Day 1 and at 6, 12, and 24 months after completion of the primary regimen <u>Cohort 2b:</u> Ad26.COV2.S 5×10^{10} vp in a 2-dose primary regimen (Day 1 and Day 57) with or without a single booster vaccination at 6, 12 or 24 months after completion of the primary regimen Placebo on Day 1, Day 57, and at 6, 12, and 24 months after completion of the primary regimen	Gp 3: 30 Gp 4: 30 Gp 5: 15 <u>Cohort 2b</u> Planned: Gp 1: 30 Gp 2: 30 Gp 3: 30 Gp 4: 30 Gp 5: 15 <u>Cohort 3</u> Gp 1: 81 Gp 2: 80 Gp 3: 82

VAC31518COV1002 Not Applicable 12 August 2020 Ongoing	JPN: 3	Phase 1 Randomised, double-blind, placebo-controlled Healthy adults aged ≥20 to ≤55 years and adults in good health with or without stable underlying conditions aged ≥65 years To assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 dose levels, 5×10^{10} vp and 1×10^{11} virus particles (vp), administered intramuscularly (IM) as 2-dose schedule in healthy adults aged ≥20 to ≤55 years and ≥65 years in good health with or without stable underlying conditions	Planned: 250	Ad26.COV2.S: 1×10^{11} vp/mL; Placebo: 0.9% NaCl solution (IM injections) Cohort 1 Days 1, 57: • Gp 1: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp • Gp 2: Ad26.COV2.S 1×10^{11} vp, Ad26.COV2.S 1×10^{11} vp • Gp 3: placebo, placebo Cohort 2 Days 1, 57: • Gp 1: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp • Gp 2: Ad26.COV2.S 1×10^{11} vp, Ad26.COV2.S 1×10^{11} vp • Gp 3: placebo, placebo	<u>Cohort 1</u> Gp 1: 51 Gp 2: 50 Gp 3: 24 <u>Cohort 2</u> Planned: Gp 1: 50 Gp 2: 50 Gp 3: 25
VAC31518COV2001 2020-002584-63 31 August 2020 Ongoing	DEU[5], NLD, ESP, and other countries to be determined[4]: Number of	Phase 2a Randomised, double-blind, placebo-controlled Healthy adults aged 18 to 55 years inclusive, adults in good or stable health aged 65 years and older and	Planned: Adults: 625 Adolescents: 660	Ad26.COV2.S: 1×10^{11} vp/mL; Placebo: 0.9% NaCl solution (IM injections) Adults Days 1, 57, and 4 months post	<u>Planned</u>: <u>Adults</u> Gp 1: 75 Gp 2: 75 Gp 3: 75

	centers to be determined	healthy adolescents aged 12 to 17 years inclusive <u>Adults</u> To assess the humoral immune response to 3 dose levels ($5x10^{10}$ vp, $2.5x10^{10}$ vp, $1.25x10^{10}$ vp) of Ad26.COV2.S, administered IM as a 2-dose schedule at a 56-day interval, 28 days after Vaccination 2. To assess the humoral immune response to 2 dose levels ($1 x10^{11}$ vp and $5x10^{10}$ vp) of Ad26.COV2.S, administered IM as a single vaccination, 28 days after Vaccination 1. To assess the humoral immune response to Ad26.COV2.S at the $5x10^{10}$ vp dose level, administered IM as a 2-dose schedule at a 28-day and at an 84-day interval, 28 days after Vaccination 2. To assess the safety and reactogenicity of Ad26.COV2.S, administered IM at several dose levels, as a 2-dose or a single-dose schedule. <u>Adolescents</u> To assess the safety and reactogenicity of Ad26.COV2.S, administered IM at the $2.5x10^{10}$ and		vaccination 2 (Injection 3)6 : • Gp 1: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp • Gp 2: Ad26.COV2.S 2.5×10^{10} vp, Ad26.COV2.S 2.5×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp • Gp 3: Ad26.COV2.S 1.25×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp • Gp 4: Ad26.COV2.S 1×10^{11} vp, placebo, Ad26.COV2.S 1.25×10^{10} vp7 • Gp 5: Ad26.COV2.S 5×10^{10} vp, placebo, Ad26.COV2.S 1.25×10^{10} vp[7] • Gp 6: Placebo, placebo, placebo Days 1, 29, and 4 months post vaccination 2 (Injection 3)[6]: • Gp 7:	Gp 4: 75 Gp 5: 75 Gp 6: 25 Gp 7: 50 Gp 8: 25 Gp 9: 50 Gp 10: 25 Gp 11: 50 Gp 12: 25 <u>Adolescents</u> Gp A: 150 Gp B: 150 Gp C: 30 Gp D: 150 Gp E: 150 Gp F: 30

		$5x10^{10}$ vp dose level, as a 2-dose or a 1-dose schedule. *If the safety profile of the $5x10^{10}$ vp dose level in adolescents is not found to be acceptable only the hypotheses on noninferiority (NI) below that are related to the $2.5x10^{10}$ vp dose level in adolescents will be tested.* To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S $5x10^{10}$ vp in adolescents vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp in adults If the above is demonstrated, then: To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S $2.5x10^{10}$ vp in adolescents vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp in adults To demonstrate NI of immune responses induced by 2 doses of Ad26.COV2.S $5x10^{10}$ vp in adolescents vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp in adults If the above is demonstrated, then to demonstrate the following in sequential order: • NI after 2-doses of Ad26.COV2.S $5x10^{10}$ vp in adolescents vs 2 doses of Ad26.COV2.S $5x10^{10}$ vp in adults		Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp • Gp 8: Placebo, placebo, placebo • Gp 11: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp • Gp 12: Placebo, placebo, placeboDays 1, 85, and 4 months post vaccination 2 (Injection 3)[6]: • Gp 9: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 1.25×10^{10} vp • Gp 10: Placebo, placebo, placebo <u>Adolescents</u> Days 1, 57, and 12 months post vaccination 1 (Injection 3)6: • Gp A: Ad26.COV2.S 2.5×10^{10} vp, placebo, Ad26.COV2.S 2.5×10^{10} vp	

		• NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp in adolescents vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp in adults • NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp in adolescents vs 2 doses of Ad26.COV2.S $5x10^{10}$ vp in adults		• Gp B: Ad26.COV2.S 2.5×10^{10} vp, Ad26.COV2.S 2.5×10^{10} vp, Ad26.COV2.S 2.5×10^{10} vp • Gp C: Placebo, placebo, placebo • Gp D: Ad26.COV2.S 5×10^{10} vp, placebo, Ad26.COV2.S 5×10^{10} vp • Gp E: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp • Gp F: Placebo, placebo, placebo	
VAC31518COV3001 Not applicable 21 September 2020 Ongoing	USA, ZAF, BRA, COL, MEX, CHL, PER, ARG: 225	Phase 3 Randomised, double-blind, placebo-controlled Stages 1a: Participants aged ≥18 to <60 years without relevant[10] comorbidities. Stage 1b: Participants aged ≥18 to <60 years with or without relevant[10] comorbidities. Stage 2a: Participants aged ≥60 years without relevant[10] comorbidities.	Planned: 40,000	Ad26.COV2.S: 1×10^{11} vp/mL; Placebo: 0.9% NaCl solution (IM inject injections) Group 1: Ad26.COV2.S 5×10^{10} vp Group 2: Placebo	Planned: Gp 1: 20,000 Gp 2: 20,000

		Stage 2b: Participants aged ≥60 years with or without relevant[10] comorbidities. To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[8], moderate to severe/critical COVID-19[9], as compared to placebo, in SARS-CoV-2 seronegative adults.			
VAC31518COV3009 2020-003643-29 16 November 2020 Ongoing	BEL, BRA, COL, FRA, DEU, PHL, ZAF, ESP, GBR, USA: 100-120	Phase 3 Randomised, double-blind, placebo-controlled Health adults ≥18 years of age To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[8], moderate to severe/critical coronavirus disease-2019 (COVID-19)[9], as compared to placebo, in SARS-CoV-2 seronegative adults	Up to 30,000	Ad26.COV2.S: 1×10^{11} vp/mL; Placebo: 0.9% NaCl solution (IM injections) Days 1, 57: • Gp 1: Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp, • Gp 2: Placebo, placebo	Planned: Gp 1: Up to 15,000 Gp 2: Up to 15,000

Abbreviations: Ad26 = adenovirus type 26; ARG = Argentina; AUS = Australia, BEL = Belgium; BRA = Brazil; COVID-19 = coronavirus disease-2019; CAN = Canada, CHL = Chile; COL = Colombia; DEU = Germany; ESP = Spain; FIN = Finland; FRA = France, Gp = group; GRB = Great Britain; IM = intramuscular; ITA = Italy; MEX = Mexico; N/A; not applicable; NLD = The Netherlands; PER = Peru; PHL = Philippines; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; USA = United States of America; vp = virus particles; ZAF =South Africa.

1. Available information is included up to a cut-off date of 22 January 2021.
2. Ad26.COV2.S is also known as Ad26COVS1.
3. In Belgium, only 65-75-year-old subjects are enrolled.
4. Countries to enroll adolescents are under discussion.
5. In Germany, no adolescents will be enrolled.
6. Antigen presentation
7. 6 Months after Vaccination 1 in the single-dose regimens (Groups 4 and 5).
8. Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result using a PCR-based or other molecular diagnostic test.
9. Per case definition for moderate to severe/critical COVID-19
10. Relevant comorbidities are comorbidities that are associated with increased risk of progression to severe COVID-19.

2.4.2. Pharmacokinetics

According to the Guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005), pharmacokinetic studies are usually not requested for vaccines.

2.4.3. Pharmacodynamics

Pharmacodynamics relates to investigation of immunogenicity.

There is no established immunological correlates of protection (ICP) against COVID-19. Both the humoral and cellular immune responses are thought to be involved in the protection against COVID-19, but their respective contribution in the protection or in the progression to/susceptibility of disease, and severe disease, are still poorly understood.

Binding and neutralising antibody responses induced by Ad26.COV2.S vaccination correlate with protection as demonstrated in NHP and Syrian hamster challenge studies.

Mechanism of action

COVID-19 Vaccine Janssen (Ad26.COV2.S) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a SARS-CoV-2 full-length spike (S) glycoprotein in a stabilised conformation. Following administration, the S glycoprotein of SARS-CoV-2 is transiently expressed, stimulating both neutralising and other functional S-specific antibodies, as well as cellular immune responses directed against the S antigen, which may contribute to protection against COVID-19.

Immunogenicity studies

The immunogenicity data available so far were generated from a Phase 1/2a FIH trial conducted in Belgium and in the US (VAC31518COV1001), a Phase 1 trial conducted in Japan (VAC31518COV1002), a Phase 2 trial conducted in Spain, the Netherlands, Germany, UK (VAC31518COV2001), and one of the Phase 3 trials (VAC31518COV3001). No immunogenicity results are available for the second ongoing VAC31518COV3009 Phase 3 trial. Data from all trials are interim results.

Both the immunogenicity assays and the studies (design and results) are discussed in the next sub-sections.

Assays used to evaluate immunogenicity

Depending on the study, the main immunogenicity objectives of the ongoing studies are to assess humoral immune responses in terms of neutralising antibodies, measured by wtVNA, and of S-specific binding antibodies, measured by S-ELISA, as well as to assess cellular immune responses, measured by ICS and/or ELISpot. In VAC31518COV1001 and VAC31518COV1002 studies, and in participants at selected sites in study VAC31518COV3001, the presence of neutralising antibodies to the Ad26 vector backbone was measured using the Ad26 VNA. Additional antibody functionality has been investigated by means of ADCP. An SARS-CoV-2 N-ELISA was used for the detection of asymptomatic infection.

Timepoints for blood samples were variable across studies. Samples were taken at baseline and 28 days post-vaccination. Additional samples were also taken, including at days 14, 56, 70, or 85 days as

well as 6 and 12-14 months post-first vaccination in the VAC31518COV1001 and VAC31518COV2001 study studies.

An overview of the immunological assays used (or that will be used) in clinical studies is presented in the Table below.

Table 4. Summary of Immunogenicity assays

Assay	Purpose
Humoral Immunogenicity	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S protein and, if such an assay can be developed, SARS-CoV-2 N protein
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other strain), as measured by an alternative neutralization assay (different from the VNA used for the secondary endpoint)
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Cellular Immunogenicity	
Flow cytometry (ICS)	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by ICS including $CD4^+/CD8^+$, IFNγ, IL-2,TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers
ELISpot	IFNγ and IL-4 responses to SARS-CoV-2 S protein peptides by PBMCs, based on single ELISpot
Gene expression analysis	Analysis of gene expression by RNA transcript profiling and/or analysis of protein translates, in cells or whole blood stimulated with SARS-CoV-2 S protein peptides or in unstimulated cells or whole blood (ex vivo)
Cytokine profiling (ELISA or multiplexed arrays)	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells or whole blood stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells or whole blood, by ELISA or multiplexed arrays and confirmation by functional in vitro assays
T and B cell phenotyping	Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube isolated PBMCs)

ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot (assay); ICS = intracellular cytokine staining; IFNγ = interferon gamma; Ig = immunoglobulin; IL = interleukin; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha; VNA = virus neutralization assay.

Sample interpretation and responder definitions were as follows:

Table 5. Overview of sample interpretation

Assay	Sample Interpretation (Positive/Negative)	Responder Definition Post Vaccination Sample: Baseline Sample Negative	Responder Definition Post Vaccination Sample: Baseline Sample Positive
SARS-CoV-2 S-ELISA			
All studies	Positive if result >LLOQ	Responder if positive	Responder if ≥4-fold increase from baseline
SARS-CoV-2 wtVNA			
All studies	Positive if result >LLOQ	Responder if positive	Responder if ≥4-fold increase from baseline
SARS-CoV-2 S ICS			
General rules for COV1001 and COV2001	Positivity was based on comparisons of the percentage of T cells with positive cytokine staining between the experimental well and the negative control well. Positivity was determined for each cytokine subset. If at least one cytokine subset was positive, the overall peptide pool (S1 or S2) was considered positive.	The responder status of a participant was determined for each cytokine separately on the background-subtracted percentages for the combined peptide pools (ie, sum of S1 and S2). For a given time point, if a responder status was achieved based on either cytokine, then the participant was considered a responder at that time point. For a given time point, a participant was considered a responder when either of the following conditions stated below were satisfied.	
COV1001, COV2001	*Assessment of Th1/Th2 response ratio.* Based on the combined SARS-Cov2-S peptide pool, and using post baseline time points only, a Th1/Th2 response ratio was calculated for samples that satisfied at least one of the following two conditions: • a Th1 response ("IFN-g or IL2 NOT TH2") that is both positive and ≥2 x LLOQ, OR • a Th2 response ("IL4 or IL5 or IL13 and CD40L") that is both positive and ≥2 x LLOQ For the purposes of the Th1/Th2 ratio analysis, the LLOQ is 0.022% for both cell populations (Th1 and Th2). If both cell populations (Th1 and Th2) were positive and ≥2 x LLOQ, then the ratio of Th1/Th2 was calculated as a numerical result. If only one cell population (either Th1 or Th2) was positive and ≥2 x LLOQ, then the following rules were used to determine a qualitative assessment of the Th1/Th2 ratio: • If one cell population is positive and the other is negative, then the positive cell population is greater than the negative cell population: if the Th1 response is positive and the Th2 response is negative, then the Th1/Th2 ratio will be set to ">1". If the Th1 response is negative and the Th2 response is positive, then the Th1/Th2 ratio will be set to "<1". • If both cell populations are positive, then the cell population that is ≥2 x LLOQ is greater than the cell population that is <2 x LLOQ: if the Th1 response is ≥2 x LLOQ and the Th2 response is <2 x LLOQ, then the Th1/Th2 ratio will be set to ">1". If the Th1 response is < 2 x LLOQ and the Th2 response is ≥2 x LLOQ, then the Th1/Th2 ratio will be set to "<1".		
SARS-CoV-2 S-specific IFN-γ ELISpot			
COV1001	Positive if result >LLOQ	Responder if positive	Responder if baseline value >LOD and ≥3-fold increase from baseline
SARS-CoV-2 S-specific IL-4 ELISpot			
COV1001	Positive if result >LOD	Responder if positive	Responder if: • the baseline sample value is ≤LOD and the post-baseline sample is >LOD • the baseline sample value is ≤LLOQ and the post-baseline sample is >LLOQ • the baseline sample value is >LLOQ and the post-baseline sample value ≥2-fold increase from the baseline sample value
Ad26 VNA			
COV1001	Positive if result >LLOQ	Not applicable	Not applicable
SARS-CoV-2 N serology assay (N Protein Binding Antibodies)			
COV3001	Positive if cut-off index >1.0	Not applicable	Not applicable

2.4.3.1.1. First-in-human VAC31518COV1001 study

In the following sections of this report, the vaccine groups will be abbreviated as follows:

- 5×10^{10}, 5×10^{10} vp group: Ad26.COV2.S 5×10^{10} vp, followed by Ad26.COV2.S 5×10^{10} vp
- 5×10^{10} vp, PL group: Ad26.COV2.S 5×10^{10} vp, followed by placebo
- 1×10^{11}, 1×10^{11} vp group: Ad26.COV2.S 1×10^{11} vp, followed by Ad26.COV2.S 1×10^{11} vp
- 1×10^{11} vp, PL group: Ad26.COV2.S 1×10^{11} vp, followed by placebo
- PL, PL group: placebo, followed by placebo

Cohort 1a was conducted for dose selection in young adults and Cohort 3 in the older adults. The selection of the optimal dose level and schedule was to be based on the safety and immunogenicity results observed in baseline SARS-CoV-2 seronegative participants.

Immunogenicity evaluation

Venous blood samples are to be collected at baseline, at 14, 28, 56 (vaccination 2), 70, 84 days post-dose 1, and at months 6 and 12 post-dose 2 for the assessment of humoral and cellular immune responses.

For purposes of analysis, the following populations are defined:

FAS: The full analysis set will include all participants with at least one vaccine administration documented.

PPI: The per protocol immunogenicity population will include all randomised and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes.

Analysis of the immunogenicity results was based on the per protocol immunogenicity population (Cohort 1a) or the full analysis set (Cohort 3), consisting of all randomised and vaccinated participants for whom immunogenicity data were available.

Cohort 1a (Adults aged ≥18-≤55 years)

The data provided by the applicant are the following:

- SARS-CoV-2 neutralising antibodies and S protein binding antibodies at baseline and Days 29, 57, 71 and 85.
- Ad26 neutralising antibodies at baseline and Day 57.
- ADCP and T cell responses (ICS) at baseline, Day 15 and Day 29.
- IFN$_{\gamma}$ and IL-4 responses (ELISpot) at baseline and Day 15.

(i) Humoral responses

Neutralising Antibody Responses to SARS-CoV-2:

Neutralising antibodies to wt SARS-CoV-2 were measured in a wtVNA assay. Samples of 25 participants (random subset) per group were analysed.

Fifteen participants in Cohort 1a were SARS CoV-2 seropositive at baseline and only one of these was in the subset of 125 participants analyzed by wtVNA. Detectable levels of neutralising antibodies were observed in a minority of participants at baseline.

Descriptive statistics of the actual values (GMTs with corresponding 95% CIs) and percentage of responders over time are provided by vaccination group in the Table below.

Table 6. SARS-CoV-2 neutralising wtVNA

	Ad26 5e10, Ad26 5e10	Ad26 5e10, PL	Ad26 1e11, Ad26 1e11	Ad26 1e11, PL	PL, PL
Analysis set: PPI Population	74	75	74	71	75
Baseline					
N	25	25	25	25	25
Geometric Mean (95% CI)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (.; .)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%)	3 (12%)	0	2 (8%)	1 (4%)	1 (4%)
(95% CI)	(3%; 31%)	(0%; 14%)	(1%; 26%)	(0; 20)	(0; 20)
Titer ≥ 100 n (%)	0	0	1 (4%)	1 (4%)	0
(95% CI)	(0%; 14%)	(0%; 14%)	(0%; 20%)	(0; 20)	(0; 14)
Day 29					
N	25	24	25	25	25
Geometric Mean (95% CI)	224 (168; 298)	224 (158; 319)	354 (220; 571)	215 (169; 273)	< LLOQ (.; .)
Positive sample n (%)	25 (100%)	23 (96%)	24 (96%)	25 (100%)	0
(95% CI)	(86%; 100%)	(79%; 100%)	(80%; 100%)	(86; 100)	(0; 14)
Titer ≥ 100 n (%)	19 (76%)	21 (88%)	23 (92%)	24 (96%)	0
(95% CI)	(55%; 91%)	(68%; 97%)	(74%; 99%)	(80; 100)	(0; 14)
GMI (95% CI) from Baseline	3.8 (2.8; 5.0)	4.0 (2.9; 5.5)	5.7 (3.9; 8.5)	3.6 (2.8; 4.6)	1.0 (1.0; 1.0)
Responders n/N* (%) (95% CI)	22/25 (88%) (69%; 97%)	23/24 (96%) (79%; 100%)	23/25 (92%) (74%; 99%)	24/25 (96%) (80; 100)	0/25 (0; 14)
Day 57					
N	25	25	24	24	23
Geometric Mean (95% CI)	288 (221; 376)	310 (228; 422)	488 (334; 714)	370 (268; 511)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%)	25 (100%)	25 (100%)	24 (100%)	24 (100%)	2 (9%)
(95% CI)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(86; 100)	(1; 28)
Titer ≥ 100 n (%)	25 (100%)	25 (100%)	24 (100%)	24 (100%)	0
(95% CI)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(86; 100)	(0; 15)
GMI (95% CI) from Baseline	4.9 (3.7; 6.3)	5.4 (3.9; 7.3)	7.6 (5.6; 10.4)	6.2 (4.4; 8.5)	1.0 (1.0; 1.0)
Responders n/N* (%) (95% CI)	24/25 (96%) (80%; 100%)	25/25 (100%) (86%; 100%)	23/24 (96%) (79%; 100%)	23/24 (96%) (79; 100)	1/23 (4%) (0; 22)
Day 71					
N	24	24	25	24	22
Geometric Mean (95% CI)	827 (651; 1052)	321 (237; 434)	1266 (913; 1757)	388 (303; 497)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%)	24 (100%)	24 (100%)	25 (100%)	24 (100%)	1 (5%)
(95% CI)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(86; 100)	(0; 23)
Titer ≥ 100 n (%)	24 (100%)	24 (100%)	25 (100%)	24 (100%)	0
(95% CI)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(86; 100)	(0; 15)
GMI (95% CI) from Baseline	13.9 (10.9; 17.7)	5.5 (4.1; 7.5)	19.8 (15.3; 25.7)	6.7 (5.2; 8.6)	1.0 (1.0; 1.0)
GMI (95% CI) from Pre-Dose 2	2.9 (2.3; 3.8)	1.0 (0.8; 1.2)	2.6 (2.0; 3.4)	1.1 (0.9; 1.3)	1.0 (1.0; 1.0)
Responders n/N* (%) (95% CI)	24/24 (100%) (86%; 100%)	24/24 (100%) (86%; 100%)	25/25 (100%) (86%; 100%)	24/24 (100%) (86; 100)	1/22 (5%) (0; 23)
Day 85					
N	24	24	24	24	22
Geometric Mean (95% CI)	849 (664; 1086)	338 (230; 496)	1229 (886; 1706)	377 (283; 503)	< LLOQ (< LLOQ; 61)
Positive sample n (%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	1 (5%)
(95% CI)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(0%; 23%)
Titer ≥ 100 n (%)	24 (100%)	24 (100%)	24 (100%)	23 (96%)	1 (5%)
(95% CI)	(86%; 100%)	(86%; 100%)	(86%; 100%)	(79%; 100%)	(0%; 23%)
GMI (95% CI) from Baseline	14.3 (11.2; 18.3)	5.8 (4.0; 8.6)	19.2 (14.3; 25.7)	6.5 (4.9; 8.7)	1.2 (0.8; 1.8)
GMI (95% CI) from Pre-Dose 2	2.9 (2.1; 3.8)	1.1 (0.8; 1.5)	2.4 (1.8; 3.2)	1.0 (0.9; 1.2)	1.2 (0.8; 1.8)
Responders n/N* (%) (95% CI)	24/24 (100%) (86%; 100%)	24/24 (100%) (86%; 100%)	24/24 (100%) (86%; 100%)	24/24 (100%) (86%; 100%)	1/22 (5%) (0%; 23%)

Key: CI = confidence interval. GMI = geometric mean increase. N = number of subjects with data. N* = number of subjects with data at baseline and at that time point. Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample and Responders. Positive sample refers to a quantifiable response (sample interpretation). Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp; PL: Placebo. The assay status is: "qualified". The assay range may change as the assay becomes validated.

Binding Antibody Responses Against SARS-CoV-2 S Protein:

Binding antibodies to the SARS-CoV-2 S protein were measured by ELISA. Samples of 75 participants per group were analysed.

Out of the 15 participants in Cohort 1a were SARS CoV-2 seropositive at baseline, 2 were defined as seropositive by screening serology alone, being negative by baseline S-ELISA.

Descriptive statistics of the actual values (GMTs with corresponding 95% CIs) and percentage of positive samples over time are provided by vaccination group in the Table below.

Table 7. S-ELISA

	Ad26 5e10, Ad26 5e10	Ad26 5e10, PL	Ad26 1e11, Ad26 1e11	Ad26 1e11, PL	PL, PL
Analysis set: PPI Population	74	75	74	71	76
Baseline					
N	73	75	74	71	76
Geometric Mean (95% CI)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	3 (4%) (1%; 12%)	5 (7%) (2%; 15%)	2 (3%) (0%; 9%)	2 (3%) (0%; 10%)	1 (1%) (0%; 7%)
Day 29					
N	72	69	74	67	72
Geometric Mean (95% CI)	586 (445; 771)	478 (379; 603)	788 (628; 988)	625 (505; 773)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	71 (99%) (93%; 100%)	69 (100%) (95%; 100%)	74 (100%) (95%; 100%)	67 (100%) (95%; 100%)	2 (3%) (0%; 10%)
GMI (95% CI) from Baseline	10.1 (8.1; 12.6)	8.8 (7.1; 10.8)	14.8 (12.2; 18.1)	12.3 (9.9; 15.2)	1.1 (0.9; 1.2)
Responders n/N* (%) (95% CI)	70/71 (99%) (92%; 100%)	68/69 (99%) (92%; 100%)	74/74 (100%) (95%; 100%)	66/67 (99%) (92%; 100%)	1/72 (1%) (0%; 7%)
Day 57					
N	74	73	74	67	70
Geometric Mean (95% CI)	786 (610; 1012)	662 (518; 844)	1059 (873; 1286)	882 (712; 1092)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	74 (100%) (95%; 100%)	73 (100%) (95%; 100%)	74 (100%) (95%; 100%)	67 (100%) (95%; 100%)	3 (4%) (1%; 12%)
GMI (95% CI) from Baseline	13.5 (10.8; 16.9)	12.2 (9.7; 15.4)	19.9 (16.8; 23.7)	16.7 (13.3; 20.9)	1.1 (0.9; 1.4)
Responders n/N* (%) (95% CI)	73/73 (100%) (95%; 100%)	72/73 (99%) (93%; 100%)	74/74 (100%) (95%; 100%)	65/67 (97%) (90%; 100%)	2/70 (3%) (0%; 10%)
Day 71					
N	70	67	71	62	65
Geometric Mean (95% CI)	2015 (1662; 2442)	612 (471; 795)	2656 (2208; 3196)	921 (735; 1154)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	70 (100%) (95%; 100%)	67 (100%) (95%; 100%)	71 (100%) (95%; 100%)	62 (100%) (94%; 100%)	3 (5%) (1%; 13%)
GMI (95% CI) from Baseline	35.9 (29.9; 43.0)	11.4 (8.9; 14.6)	49.9 (41.9; 59.5)	17.4 (13.6; 22.1)	1.1 (0.9; 1.4)
GMI (95% CI) from Pre-Dose 2	2.6 (2.2; 3.1)	1.0 (0.9; 1.0)	2.5 (2.1; 2.8)	1.0 (0.9; 1.2)	1.0 (1.0; 1.0)
Responders n/N* (%) (95% CI)	69/69 (100%) (95%; 100%)	67/67 (100%) (95%; 100%)	71/71 (100%) (95%; 100%)	60/62 (97%) (89%; 100%)	2/65 (3%) (0%; 11%)
Day 85					
N	72	70	70	64	67
Geometric Mean (95% CI)	1994 (1674; 2375)	658 (502; 862)	2465 (2063; 2946)	965 (772; 1205)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	72 (100%) (95%; 100%)	70 (100%) (95%; 100%)	70 (100%) (95%; 100%)	64 (100%) (94%; 100%)	5 (7%) (2%; 17%)
GMI (95% CI) from Baseline	35.7 (28.9; 43.9)	12.1 (9.3; 15.7)	46.3 (39.3; 54.5)	18.2 (14.4; 23.1)	1.2 (1.0; 1.5)
GMI (95% CI) from Pre-Dose 2	2.5 (2.1; 3.1)	1.0 (0.9; 1.2)	2.3 (2.0; 2.7)	1.1 (1.0; 1.2)	1.1 (1.0; 1.2)
Responders n/N* (%) (95% CI)	70/71 (99%) (92%; 100%)	69/70 (99%) (92%; 100%)	70/70 (100%) (95%; 100%)	62/64 (97%) (89%; 100%)	4/67 (6%) (2%; 15%)

Key: CI = confidence interval. GMI = geometric mean increase. N = number of subjects with data. N* = number of subjects with data at baseline and at that time point. Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample and Responders. Positive sample refers to a quantifiable response (sample interpretation).Note: Ad26 5e10: Ad26.COV2.S $5x10^{10}$ vp; Ad26 1e11: Ad26.COV2.S $1x10^{11}$ vp; PL: Placebo. The assay status is: "qualified". The assay range may change as the assay becomes validated.

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Neutralising antibody titers correlated highly with binding antibody concentrations at Day 29 and Day 71. The Spearman correlation at both timepoints was >0.80.

Functional Antibody Characterisation:

Antibody-dependent cellular phagocytosis of SARS-CoV-2 trimeric Spike antigen was measured by an ADCP assay. Samples of 75 participants per group were analysed.

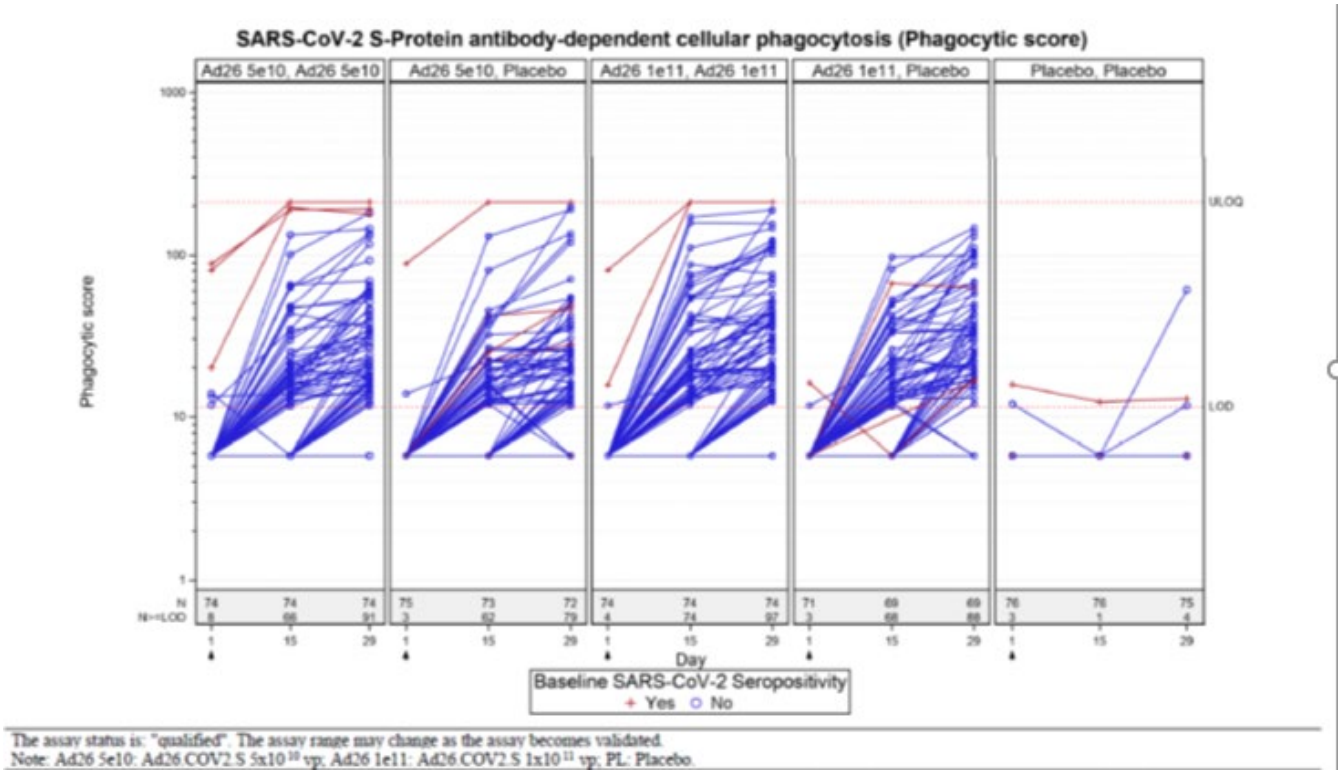


Figure 4. SARS-CoV-2 S-ADCP (phagocytic score)

Correlation analysis demonstrated a positive correlation between ADCP (phagocytic score) and neutralising antibody titers (IC50), with a Spearman correlation of 0.75. A strong positive correlation between phagocytic score and binding antibody titers (EU/mL) was also demonstrated (Spearman correlation =0.856).

Pre-existing immunity and Responses to Ad26 Backbone:

Neutralising antibodies to the Ad26 backbone vector were measured using the Ad26 VNA at baseline and prior to second vaccination on Day 57.

Four participants had pre-existing levels of Ad26-neutralising antibodies ≥LLOQ.

At Day 57 Ad26-neutralising antibodies ≥LLOQ were detected in more than 95% of participants in the active vaccine groups, compared to 9% of those in the PL, PL group.

Correlation analysis of Ad26 neutralising antibodies pre-dose 2 vs. SARS-CoV-2 neutralising antibodies post-dose 2 showed a poor correlation between the two variables (r=-0.25 at Day 71 and r=-0.29 at Day 85).

Neutralising Antibody Responses to SARS-CoV-2 B.1.1.7 lineage (variant 20I/501Y.V1):

Neutralising antibodies capable of inhibiting live virus infections by the SARS-CoV-2 B.1.1.7 lineage (variant 20I/501Y.V1) were assessed in samples of Cohort 1a as part of the exploratory analyses with a non-qualified assay. No LLOQ was determined and no responder definition is applied. Neutralising antibody titers against SARS-CoV-2 are expressed as IC50 units.

Samples from VAC31518COV1001 Cohort 1a were selected for the measurement of neutralising antibodies directed against the B.1.1.7 lineage. In particular, samples showing high titers in the

Victoria/1/2020 wtVNA were selected 28 days post-dose 1 (Day 29, n=8), 70 days post-dose 1 (i.e. 14 days post-dose 2, Day 71, n=24).

Neutralising antibody titers against SARS-CoV-2 B1.1.17 were detectable in all samples from the active groups, while all placebo samples were below detection.

For the 6 Day 29-samples of the 5×10^{10} vp, PL group, nAb GMT observed in the Victoria 1/2020 VNA was 573 (95% CI: 268-1,226) whereas the GMT observed in the B.1.1.7 lineage VNA was 65 (95% CI: 30-141).

For the 14 Day 71-samples of the 5×10^{10} vp, PL group, nAb GMT observed in the Victoria 1/2020 VNA was 375 (95% CI: 271-519) whereas the GMT observed in the B.1.1.7 lineage VNA was 113 (95% CI: 82-155).

For the 6 Day 71-samples of the 5×10^{10}, 5×10^{10} vp group, nAb GMT observed in the Victoria 1/2020 VNA was 1,656 (95% CI: 1,046-2,622) whereas the GMT observed in the B.1.1.7 lineage VNA was 398 (95% CI: 282-561).

(ii) Cellular immune responses

CD4+ T and CD8+ T-cell Responses by ICS:

The induction of CD4+ and CD8+ T-cell responses was determined by ICS at baseline, Day 15 and Day 29 post-dose 1.

PBMCs were collected from a subset of participants for this analysis (n=196).

Profiles for CD4+ T cells expressing IFNγ and/or IL-2 (Th1), but not Th2 cytokines, and CD8+ T cells expressing IFNγ and/or IL-2 in response to SARS-CoV-2 S peptide stimulation are presented below.

Median CD4+ Th2 (CD4+ T cells expressing IL-4 and/or IL-5/IL-13 and CD40L) responses were undetectable at Day 1, Day 15 and Day 29 in all vaccine groups.

The Th1/Th2 ratio was above 1 for all participants in the active vaccine groups.

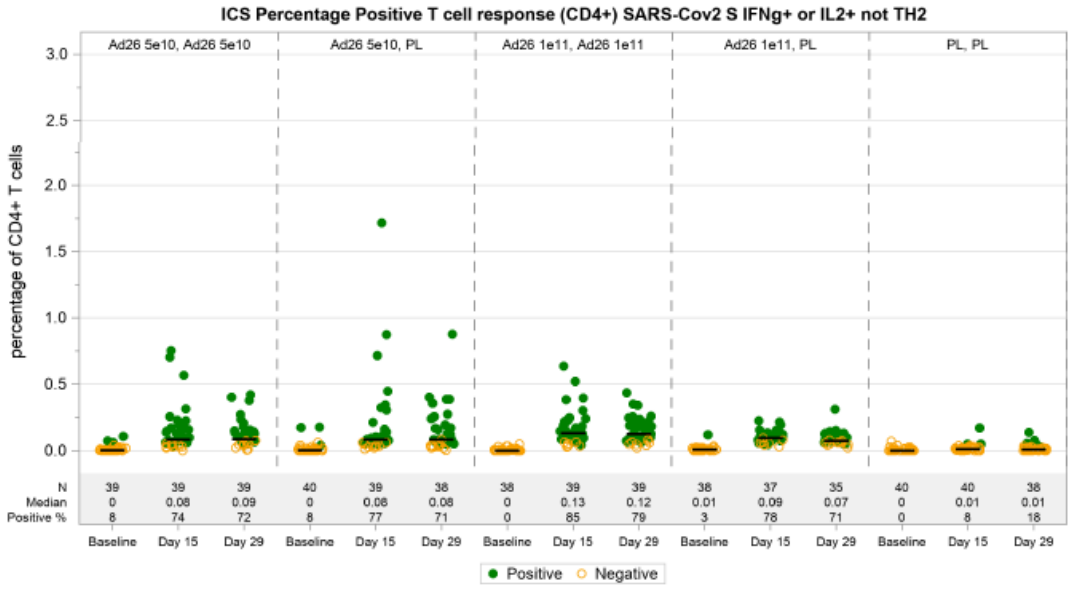
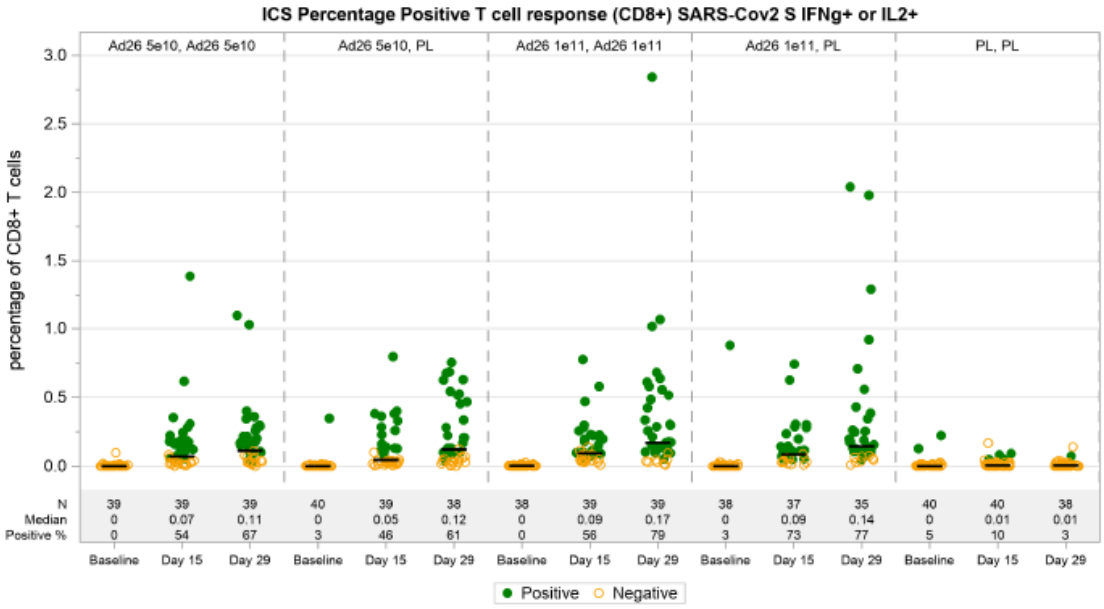


Figure 5. Percentage of CD4+ Th1 cells



Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp; PL: Placebo.
Values below 0.022% were imputed with 0.011% for purposes of visual display. Calculation are based on actual values.
The assay status is: "qualified". The assay range may change as the assay becomes validated.

Figure 6. Percentage of CD8+ Th1 cells

IFN-γ and IL-4 Responses by ELISpot:

Th1 and Th2 phenotypes were characterised by IFNγ and IL-4 ELISpot quantification, respectively, in 375 subjects. ELISpot results confirmed the results observed by the ICS method, an induction of Th1 cells responses in most of the vaccinated subjects, and overall comparable between groups.

The Th1/Th2 ratio was above 1 for all participants in the active vaccine groups.

Cohort 3 (Adults aged ≥65 years)

The data provided by the applicant are the same as for Cohort 1a, with some differences on the days at which some of the blood draws have been carried out. There are no immunogenicity data post-dose 2 except for the sentinel participants.

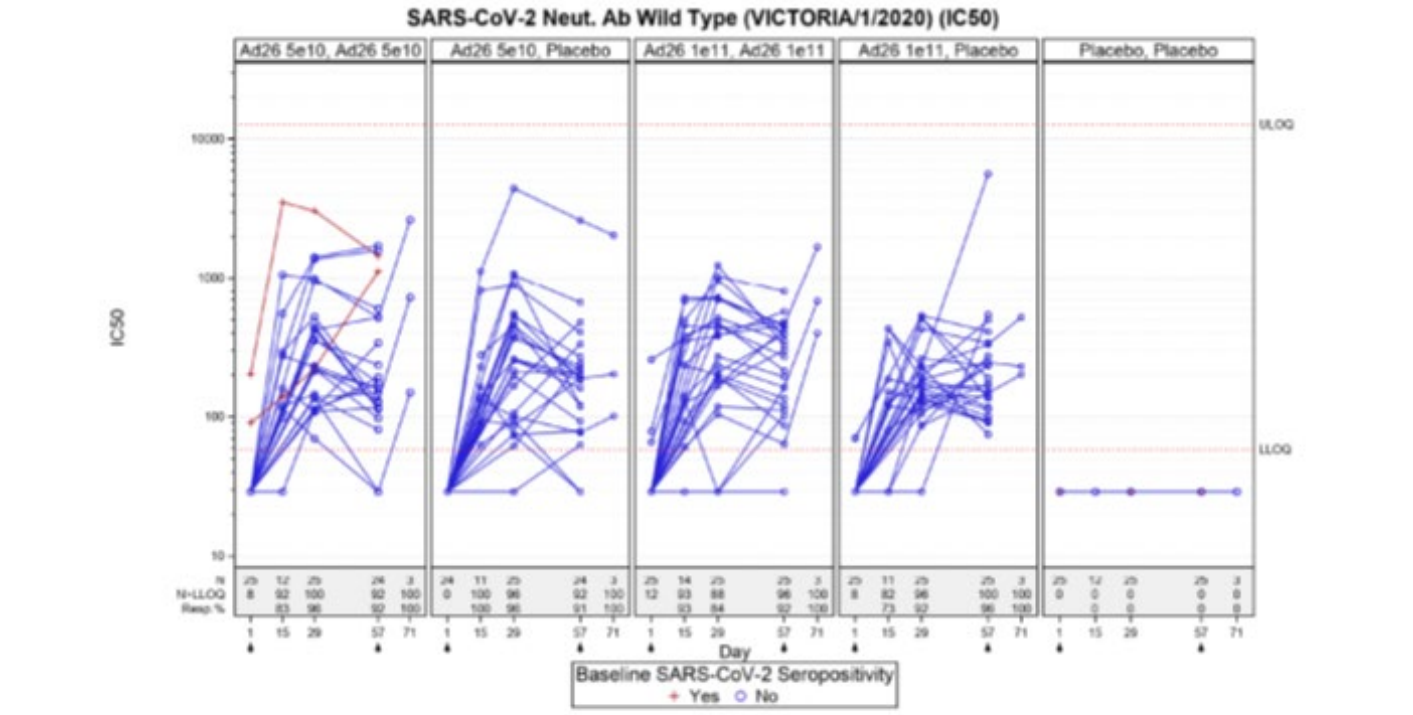
When interpreting the Day 57 results from Cohort 3, it is important to note that, due to the study pause, Day 57 blood draws for immunogenicity were delayed for the majority of participants. Data within the defined per protocol Day 57 visit window (57 ±3-7 days post vaccination) are available for 15 participants only (n=3 per group). For the remaining participants, the actual timing of the Day 57 blood draw ranged from 86 to 107 days post-vaccination (median visit = Day 87). Therefore, data presented below for Cohort 3 are based on the FAS instead of the PPI set, ie, including data from participants out of window for the Day 57 blood samples.

(i) Humoral responses

Neutralising Antibody Responses to SARS-CoV-2:

Samples of 25 participants per group were analysed.

Neutralising antibody responses against SARS-CoV-2 over time are graphically presented in the Figure below.



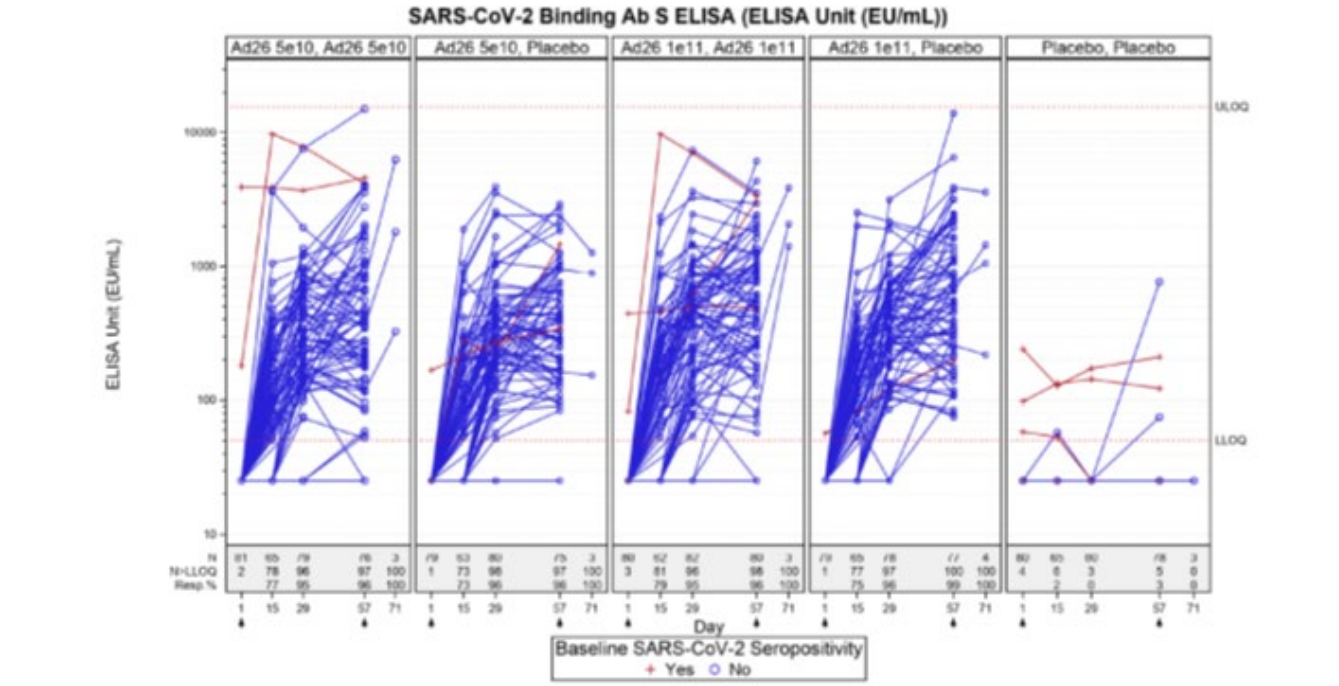
The assay status is: "qualified". The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S $5x10^{10}$ vp; Ad26 1e11: Ad26.COV2.S $1x10^{11}$ vp; PL: Placebo.

Figure 7. SARS-CoV-2 wtVNA

Binding Antibody Responses Against SARS-CoV-2 S Protein:

Samples of 80 participants per group were analysed.

Binding antibody responses against SARS-CoV-2 over time are graphically presented in the Figure below.



The assay status is: "qualified". The assay range may change as the assay becomes validated.
Ad26 5e10: Ad26.COV2.S $5x10^{10}$ vp; Ad26 1e11: Ad26.COV2.S $1x10^{11}$ vp; PL: Placebo.

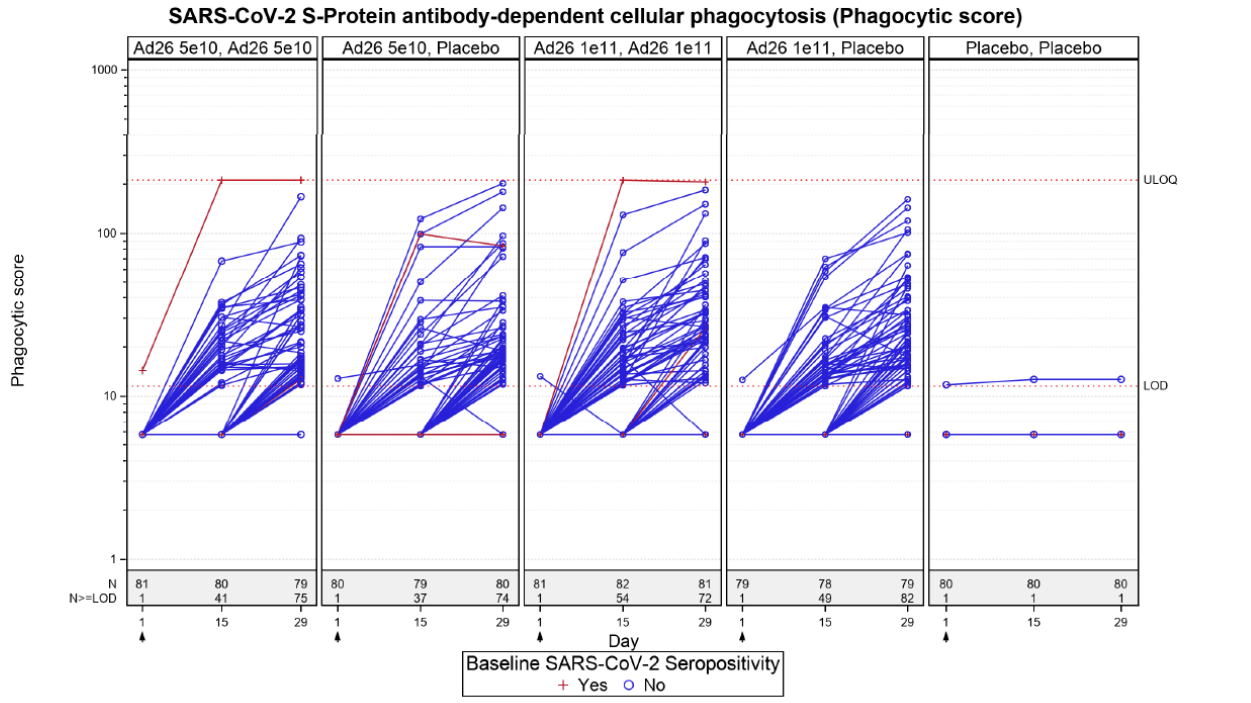
Figure 8. S-ELISA

Examination of humoral assay correlations indicated that neutralising antibody titers (IC50) correlated highly with binding antibody concentrations (ELISA units/mL) at Day 29. The Spearman correlation value was 0.72.

Functional Antibody Characterisation:

Samples of 80 participants per group were analysed.

The results from this analysis are shown in the next Figure.



The assay status is: "qualified". The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5x10 [10] vp; Ad26 1e11: Ad26.COV2.S 1x10 [11] vp; PL: Placebo.
[GIRHUM183-C3.RTF] [VAC31518\VAC31518COV1001\DBR_EUA_IMMUNO_2_JAN21_SEQUESTERED\RE_EUA_IMMUNO_2_JAN21_SEQUESTERED\PROD\GIRHUM183-C3.SAS]
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Figure 9. SARS-CoV-2 S-ADCP (phagocytic score)

Correlation analysis demonstrated a high correlation between ADCP (phagocytic score) and neutralising antibody titers (IC50), with a Spearman correlation of 0.72. A strong correlation between phagocytic score and binding antibody titers (EU/mL) was also demonstrated (Spearman correlation =0.80).

Pre-existing immunity to Ad26 Backbone:

Of the Cohort 3 participants, 23 had pre-existing levels of Ad26-neutralising antibodies.

(ii) Cellular immune responses

CD4+ T and CD8+ T-cell Responses by ICS:

PBMCs were collected from a subset of 200 participants for analysis of cellular immune responses (n=40 per group).

CD4 Th1 cells were detected at Day 15 and the proportion of positive samples slightly increase up to 28 days post-vaccination. At Day 15, the proportion of positive samples ranged from 59% to 63% and from 63% to 74% at Day 29. Median responses were also comparable between groups at Day 15 (0.07%-0.09%) and remained stable up to Day 29 (0.09%-0.10%).

Median Th2 responses were undetectable at Day 1, Day 15 and Day 29 in all vaccine groups.

The Th1/Th2 ratio was above 1 for all participants in the active vaccine groups.

CD8 Th1 cells were detected at Day 15 and their proportion further increased up to 28 days post-vaccination. Proportion of positive samples ranged between 49% and 65% at Day 29. Median responses ranged between 0.06% and 0.11%.

Regression Analyses of Antibody Responses on Demographic and Baseline Characteristics

The effect of demographic and baseline characteristics on both neutralising and binding antibody responses was examined on pooled data from Cohort 1a and Cohort 3 at Day 29 (n=198 and 598 for nAb and binding Ab, respectively), and on data from Cohort 1a at Day 57 and Day 71 (n=98 and n=278 for nAb and binding Ab, respectively). A p-value of <0.05 was taken to indicate a statistically significant effect. However, it should be noted that neutralising and binding antibody responses were observed in all subgroups and that the assessment of the clinical relevance of the observed differences between subgroups is difficult.

No statistically significant differences in neutralising and antibody responses were observed for race or BMI. Males mounted significantly lower nAb and binding Ab responses than females.

Age did not significantly impact nAb levels at any timepoint whereas older participants showed lower levels of binding Ab at Day 29 and Day 57 timepoints. At Day 71, no impact of age was observed on neutralising or binding antibody responses based on the regression analysis. However, when comparing neutralising antibody response in Cohort 1a and Cohort 3, a trend for decreased neutralising antibody response (GMTs) was observed in participants ≥65 years old compared to 18-55-year-old participants at Day 57.

Baseline SARS-CoV-2 serostatus also significantly impacted levels of neutralising and binding Ab at all 3 timepoints (with the exception of Day 71 for the binding Ab). This should be interpreted with caution since there were only a small number of baseline seropositive participants. However, this is not counter-intuitive.

Ad26.COV2.S dose level did not significantly impacted levels of nAb whereas it did for binding Ab at all 3 timepoints. As expected, number of administered active vaccine doses had a highly significant impact on both neutralising and binding Ab levels.

2.4.3.1.2. Study VAC31518COV1002

Immunogenicity evaluation

Venous blood samples were/are to be collected for determination of immune responses in Cohorts 1 and 2 at pre-specified timepoints (14- and 28-days post-dose 1, prior dose 2, 14- and 28-days post-dose 2, 6 months post-dose 2 and 12 months post-dose 1.

The data on SARS-COV-2 and Ad26 nAb for Cohort 1 were provided by the applicant.

No formal hypothesis on immunogenicity will be tested. The immunogenicity analyses will be performed on the PPI population. Immunogenicity analyses will also be done on the FAS.

Analysis of the immunogenicity results was based on the PPI population. Baseline and post-first vaccination immunogenicity results were provided in 5×10^{10} vp (n=51), 1×10^{11} vp (n=50) and placebo (n=24) groups, respectively.

Humoral immunogenicity

Neutralising Antibody Responses Against SARS-CoV-2:

Detectable baseline levels of SARS-CoV-2 IC50 titers, potentially indicative of previous SARS-CoV-2 exposure, were observed in 1 participant in the 5×10^{10} vp vaccine group, 6 participants in the 1×10^{11} vp vaccine group.

Descriptive statistics of the actual values and percentages of responders are provided by vaccine group in the table below x.

Table 8. SARS-CoV-2 neutralisation wtVNA

	Ad26 5e10	Ad26 1e11	Placebo
Analysis set: Per Protocol Immunogenicity Set	51	50	24
Baseline			
N	51	50	24
Geometric Mean (95% CI)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (NE; NE)
Positive sample n (%)	1 (2%)	6 (12%)	0
(95% CI)	(0%; 10%)	(5%; 24%)	(0%; 14%)
Titer ≥ 100 n (%)	0	2 (4%)	0
(95% CI)	(0%; 7%)	(0%; 14%)	(0%; 14%)
Day 29			
N	50	49	24
Geometric Mean (95% CI)	269 (228; 318)	375 (306; 460)	< LLOQ (NE; NE)
Positive sample n (%)	50 (100%)	49 (100%)	0
(95% CI)	(93%; 100%)	(93%; 100%)	(0%; 14%)
Titer ≥ 100 n (%)	48 (96%)	48 (98%)	0
(95% CI)	(86%; 100%)	(89%; 100%)	(0%; 14%)
Geometric mean increase (95% CI) from Baseline	4.6 (3.9; 5.4)	6.1 (4.9; 7.5)	1.0 (NE; NE)
Responders n/N* (%)	49/50 (98%)	47/49 (96%)	0/24
(95% CI)	(89%; 100%)	(86%; 100%)	(0%; 14%)
Percentage >= 4-fold, n (%)	30 (60%)	35 (71%)	0

Key: CI = confidence interval; NE = Not estimable.
N = number of subjects with data.
N* = number of subjects with data at baseline and at that time point.
Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample and Responders.
Positive sample refers to a quantifiable response (sample interpretation).
Note: Ad26 5e10: Ad26COVS1 $5x10^{10}$ vp; Ad26 1e11: Ad26COVS1 $1x10^{11}$ vp.
The assay status is: "qualified". The assay range may change as the assay becomes validated.

Pre-existing immunity to Ad26 Backbone:

Detectable baseline levels of Ad26 nAb were observed in 4 out of 125 participants.

2.4.3.1.3. Study VAC31518COV2001

In adults, the immunogenicity of Ad26.COV2.S in 1- and 2-dose vaccination regimens followed single low-dose immunisation after 4 months (2-dose regimen) or 6 months (single-dose regimen), will be evaluated across 4 dose levels and vaccination intervals ($1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp).

In adolescents, the immunogenicity of Ad26.COV2.S in a 1- and 2-dose vaccination regimen followed by a booster vaccination 12 months after the first vaccination, will be evaluated for 2 different dose levels ($5x10^{10}$ vp or $2.5x10^{10}$ vp). The applicant did not presented results for the adolescents part of this CMA.

Immunogenicity assessment

Venous blood samples are to be collected at baseline, at 14 and 28 days post-dose 1, the day of the vaccination 2 (day 57), at 7, 14 and 28 days post-dose 2, the day of the third injection (antigen presentation), at 7 and 28 days post-dose 3, at 6 months post-dose 3 and 12 months post-dose 2 for the assessment of humoral and cellular immune responses.

Venous blood samples were collected for assessment of humoral immune responses in all participants whereas cellular immune responses will be assessed in a subset of adult participants.

The data on SARS-COV-2 nAb were provided by the applicant. The immunogenicity analyses are descriptive and are performed on the PPI population. Immunogenicity analyses are also done on the FAS.

Humoral immunogenicity

Neutralising Antibody Responses Against SARS-CoV-2:

Wild-type VNA data was available from a subset of participants from Groups 1 – 6 (n=40 per vaccine groups, n= 15 for the Placebo group). Data from vaccine Groups 1 and 5 ($5x10^{10}$ vp) were pooled.

Table 9. SARS-CoV-2 neutralisation wtVNA

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10	Ad26 1e11	Placebo
Analysis set: Per Protocol Immuno Population	40	40	78	39	15
Baseline					
N	39	40	76	39	15
Geometric mean (95% CI)	< LLOQ	< LLOQ	< LLOQ (< LLOQ; < LLOQ)	< LLOQ	< LLOQ
Positive sample n (%) (95% CI)	0 (0.0; 9.0)	0 (0.0; 8.8)	2 (2.6%) (0.3; 9.2)	0 (0.0; 9.0)	0 (0.0; 21.8)
Titer ≥ 100 n (%) (95% CI)	0	0	0	0	0
Day 15					
N	23	21	46	27	9
Geometric mean (95% CI)	82 (< LLOQ; 121)	130 (88; 191)	144 (108; 190)	155 (105; 230)	< LLOQ
Difference to Ad26 5e10: GMR (95% CI)	0.6 (0.4; 0.9)	0.9 (0.6; 1.5)	-	1.1 (0.7; 1.7)	0.2 (0.2; 0.3)
Positive sample n (%) (95% CI)	15 (65.2%) (42.7; 83.6)	18 (85.7%) (63.7; 97.0)	38 (82.6%) (68.6; 92.2)	23 (85.2%) (66.3; 95.8)	0 (0.0; 33.6)
Titer ≥ 100 n (%) (95% CI)	11 (47.8%) (26.8; 69.4)	14 (66.7%) (43.0; 85.4)	31 (67.4%) (52.0; 80.5)	18 (66.7%) (46.0; 83.5)	0 (0.0; 33.6)
Geometric mean increase (95% CI) from Baseline	1.8 (1.4; 2.4)	2.5 (1.8; 3.4)	2.7 (2.2; 3.4)	3.0 (2.1; 4.1)	1.0
Difference to Ad26 5e10: GMR (95% CI)	0.7 (0.5; 0.9)	0.9 (0.6; 1.3)	-	1.1 (0.7; 1.6)	0.4 (0.3; 0.5)
Responders n/N* (%) (95% CI)	15/23 (65.2%) (42.7; 83.6)	18/21 (85.7%) (63.7; 97.0)	35/45 (77.8%) (62.9; 88.8)	23/27 (85.2%) (66.3; 95.8)	0/9 (0.0; 33.6)
Day 29					
N	39	40	78	39	15
Geometric mean (95% CI)	140 (102; 192)	173 (131; 229)	257 (216; 305)	251 (194; 326)	< LLOQ
Difference to Ad26 5e10: GMR (95% CI)	0.5 (0.4; 0.8)	0.7 (0.5; 0.9)	-	1.0 (0.7; 1.3)	0.1 (0.1; 0.1)
Positive sample n (%) (95% CI)	32 (82.1%) (66.5; 92.5)	36 (90.0%) (76.3; 97.2)	75 (96.2%) (89.2; 99.2)	38 (97.4%) (86.5; 99.9)	0 (0.0; 21.8)
Titer ≥ 100 n (%) (95% CI)	27 (69.2%) (52.4; 83.0)	29 (72.5%) (56.1; 85.4)	69 (88.5%) (79.2; 94.6)	33 (84.6%) (69.5; 94.1)	0 (0.0; 21.8)
Geometric mean increase (95% CI) from Baseline	2.7 (2.1; 3.5)	3.2 (2.5; 4.1)	4.4 (3.7; 5.2)	4.4 (3.4; 5.6)	1.0
Difference to Ad26 5e10: GMR (95% CI)	0.6 (0.5; 0.8)	0.7 (0.6; 1.0)	-	1.0 (0.8; 1.3)	0.2 (0.2; 0.3)
Responders n/N* (%) (95% CI)	31/38 (81.6%) (65.7; 92.3)	36/40 (90.0%) (76.3; 97.2)	73/76 (96.1%) (88.9; 99.2)	38/39 (97.4%) (86.5; 99.9)	0/15 (0.0; 21.8)

Key: CI = confidence interval, GMR = geometric mean ratio.
N = number of subjects with data.
N* = number of subjects with data at baseline and at that time point.
Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample, Titer >= 100 and Responders.
Positive sample refers to a quantifiable response (sample interpretation).
Note: Ad26 1.25e10: Ad26.COV2.S 1.25x10 [10] vp; Ad26 2.5e10: Ad26.COV2.S 2.5x10 [10] vp; Ad26 5e10: Ad26.COV2.S 5x10 [10] vp; Ad26 1e11: Ad26.COV2.S 1x10 [11] vp.
The assay status is: qualified. The assay range may change as the assay becomes validated.

A trend for lower positive sample rate, responder rate and GMTs was observed in subjects of 65 years of age and over, for all dose levels, when compared to the younger 18-55 years of age subjects.

2.4.3.1.4. Phase 3 study VAC31518COV3001

This section focuses on the immunogenicity assessment. See section clinical efficacy, main study, for further study description.

Blood is to be collected from all non-Immunogenicity Subset participants for humoral immunogenicity assessments at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination.

For a total of approximately 400 participants in the Immunogenicity Subset (i.e., participants at sites with access to appropriate processing facilities), blood samples are to be collected for analysis of

humoral immune responses on Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year as for the non-immunogenicity subset, and also at 18 months, and 2 years after vaccination.

During a COVID-19-episode, blood is to be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 for immunogenicity assessments (for biomarker evaluation).

A serologic test for past or current infection with SARS-CoV-2 is to be performed for all participants at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination.

Immunogenicity subset

Participants in the Immunogenicity Subset are divided into 4 groups as presented in the table below.

Table 10. Sample size and distribution of the immunogenicity subset

Study Vaccine	Subset 1a	Subset 1b	Subset 2a	Subset 2b
5×10^{10} vp	50	50	50	50
Placebo	50	50	50	50
Total	**100**	**100**	**100**	**100**

vp = virus particles
Subset 1a: healthy ≥18- to <60-year-old adults **without relevant comorbidities**, enrolled during Stage 1a.
Subset 1b: ≥18- to <60-year-old adults **with relevant comorbidities**, enrolled during Stage 1b.
Subset 2a: healthy ≥60-year-old adults **without relevant comorbidities**, enrolled during Stage 2a.
Subset 2b: ≥60-year-old adults **with relevant comorbidities**, enrolled during Stage 2b.

Correlates subset

Correlates of risk of COVID-19 will be assessed in a subset including all vaccine recipients who experience a SARS-CoV-2 event, and random samples of vaccine recipients who have not been infected. Correlates of infection or disease/disease severity, or protection will also be investigated.

No formal statistical testing of the immunogenicity data was planned. All immunogenicity analyses are to be performed on the PPI set.

Changes in planned analyses

As an increase in SARS-CoV-2 infection rate was observed during the study at specific Brazilian sites (sites BR10003, BR10004), there were concerns that regional differences in vaccine efficacy would be observed at the moment of the primary analysis. Evident reasons for these differences, outside of environmental, would be lower protection against SARS-CoV-2 viral variants and/or lower vaccine immunogenicity; therefore, the applicant decided to evaluate Ad26.COV2.S immunogenicity by measuring S-specific binding antibodies at Day 1 and Day 29 post-vaccination in participants randomly selected from these sites as well as other random Brazilian sites, South African sites, and US sites. In addition, as seroprevalence of Ad26 is known to differ in different regions, an analysis of pre-existing Ad26 immunity, measured by Ad26 neutralising antibody titers at Day 1, was also performed to determine if there was a high prevalence of pre-existing Ad26 neutralising antibodies at baseline. All these analyses were planned and performed before the database lock.

Humoral immunogenicity

Binding Antibody Responses Against SARS-CoV-2 S Protein:

At the time of primary analysis, only preliminary immunogenicity data were available. Data that are presented are those of participants randomly selected from the two main Brazilian sites as well as other random Brazilian sites (n=188, different sites), South African sites (n=118), and US sites (n=74).

Overall, similar SARS-CoV-2 S binding antibody levels and responder rates were observed across different countries and regions (see Table below).

Table 11. SARS-CoV-2 S binding Ab

	South Africa		Brazil overall		USA	
	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo
Analysis set: Immuno Set	88	30	114	74	50	24
Baseline						
N	84	30	114	74	50	24
Geometric mean (95% CI)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	4 (4.8%) (1.3; 11.7)	4 (13.3%) (3.8; 30.7)	2 (1.8%) (0.2; 6.2)	4 (5.4%) (1.5; 13.3)	1 (2.0%) (0.1; 10.6)	1 (4.2%) (0.1; 21.1)
Day 29						
N	80	28	86	49	48	23
Geometric mean (95% CI)	388 (297; 506)	< LLOQ (< LLOQ; < LLOQ)	402 (321; 505)	< LLOQ (< LLOQ; < LLOQ)	412 (306; 554)	< LLOQ (< LLOQ; < LLOQ)
Difference to USA: GMR (95% CI)	0.94 (0.63; 1.42)	-	0.98 (0.67; 1.42)	-	-	-
Positive sample n (%) (95% CI)	76 (95.0%) (87.7; 98.6)	5 (17.9%) (6.1; 36.9)	83 (96.5%) (90.1; 99.3)	5 (10.2%) (3.4; 22.2)	47 (97.9%) (88.9; 99.9)	2 (8.7%) (1.1; 28.0)
Geometric mean increase (95% CI) from Baseline	7.4 (5.7; 9.5)	1.0 (1.0; 1.1)	7.8 (6.3; 9.6)	1.0 (1.0; 1.1)	8.3 (6.2; 11.0)	1.1 (0.9; 1.4)
Responders n/N* (%) (95% CI)	71/76 (93.4%) (85.3; 97.8)	2/28 (7.1%) (0.9; 23.5)	82/86 (95.3%) (88.5; 98.7)	2/49 (4.1%) (0.5; 14.0)	47/48 (97.9%) (88.9; 99.9)	1/23 (4.3%) (0.1; 21.9)

Ad26 = adenovirus 26, CI = confidence interval, GMI = Geometric Mean Increase, GMR = Geometric Mean Ratio, LLOQ = lower limit of quantification, USA = United States of America
Key:
N = number of subjects with data
N* = number of subjects with data at baseline and at that time point
Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample and Responders.
Positive sample refers to a quantifiable response (sample interpretation).
The assay status is: "validated".

Pre-existing immunity to Ad26 Backbone:

Ad26 nAb titers at baseline were measured for participants from Brazil and the US. Among the US participants, only 2.0% in the active vaccine group and 4.2% in the placebo group, were 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 neutralising antibodies at baseline, 23 (85.2% [95% CI: 66.3; 95.8]) were vaccine responders as measured by S-ELISA at Day 29. Among

the 59 Brazilian participants with no detectable Ad26 neutralising 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 of -0.378) was observed between S binding antibody levels at Day 29 post vaccination and pre-existing Ad26 neutralising antibodies at baseline. This is consistent with the overall comparable GMT values observed at D29 post-vaccination between the US site and the Brazilian sites.

2.4.4. Discussion on clinical pharmacology

All interim immunogenicity data available were generated from a Phase 1/2a FIH trial, a Phase 1 trial, a Phase 2 trial, and a Phase 3 trial (VAC31518COV3001), up to 3 months post-dose 1. No immunogenicity results are available for the second ongoing VAC31518COV3009 Phase 3 trial. This is acceptable for the cMA, but longer follow-up data should be provided with final CSRs.

Study VAC31518COV1001 is an ongoing randomised, double-blind, placebo-controlled, Phase 1/2a multicentre first-in-human (FIH) dose selection study conducted in adults aged ≥18 to ≤55 years (n=670) and aged ≥65 years (n=375) in Belgium and in the US. Based on platform experience, the dose levels of $5x10^{10}$ vp and $1x10^{11}$ vp, both administered as a 1-dose and a 2-dose regimen, were selected. This study also includes an evaluation of a single booster vaccination.

Study VAC31518COV1002 is a randomised, double-blind, placebo-controlled, Phase 1 trial conducted in adults aged ≥20 to ≤55 years (n=125) and ≥65 years (n=125). Two dose levels were tested in a 2-dose schedule in Japan.

Study VAC31518COV2001 is an ongoing randomised, double-blind, placebo-controlled, multicentre Phase 2a study conducted in Germany, the Netherlands and Spain. Adults aged 18 to 55 years, and adults in good or stable health aged 65 years and older are being enrolled (n=625). Immunogenicity of Ad26.COV2.S in 1- and 2-dose vaccination regimen will be evaluated across a range of dose levels and vaccination intervals. A single low-dose immunisation with $1.25x10^{10}$ vp Ad26.COV2.S to mimic antigen presentation, will be administered 4 months after the second vaccination to all participants in all active vaccine groups to assess the immune memory. It is unclear why the anamnestic response will be assessed with a shorter interval between the primary vaccination and the antigen presentation for the 2-dose schedule when compared to the 1-dose schedule. This should be clarified by the applicant as soon as possible (see list of recommendations).

The design of the 4 clinical trials are overall considered adequate for the characterisation of the immune responses induced following Ad26.COV2.S administration.

In addition, Ad26.COV2.S-induced immune responses will be assessed in a subset of participants of study VAC31518COV3001 (see efficacy section for further details on the design).

Overall, the main immunogenicity objectives consisted in the assessment of humoral (neutralising and binding Ab) and cellular (Th1, Th2) immune responses, which are both thought to be involved in the protection against COVID-19. Their respective contribution in the protection or in the progression to/susceptibility of disease, and severe disease, is still poorly understood.

Timepoints for blood samples were variable across studies. Samples were taken at baseline and 28 days post-vaccination. Additional samples were also taken, among others, at days 14, 56, 70, or 84 days post-first vaccination in the VAC31518COV1001 and VAC31518COV2001 study studies. Blood will also be taken at later time-point, i.e. at months 6 and 12 post-dose 1/2. Sampling schedules are appropriate to determine the kinetic of the immune responses. The immunogenicity analyses are

descriptive and were performed on the PPI population, or on random subset of participants (VNA analysis) or on an immunogenicity set of participants at selected sites in VAC31518COV3001.

The assays used include measure of the humoral response to the S protein in terms of binding antibodies (by ELISA), functional antibodies (Virus neutralisation assay, Antibody-Dependent Phagocytosis Assay to measure Fc-mediated viral clearance), and neutralising antibodies against the Ad26 vector. Moreover, the cellular immune response (CD4+ and CD8+) induced has been characterised by two assays (ICS and ELISpot), which would allow determining whether the induced response was Th1- or Th2-polarised. Overall, the assays selected for both measures (humoral and cellular response) are endorsed. The main assays were qualified or validated. The wtMNA validation is ongoing. Additional reports and information should be provided by the applicant as soon as possible (see list of recommendations). A new SARS-CoV-2 MNA based assay was developed, using a different strain, i.e. the variant 20I/501Y.V1 (B.1.1.7 lineage). nAb assessment should also include testing against other variants of concern, at least 20H/501Y.V2, 20J/501Y.V3 and 20B/S.484K (P.2 Brazilian variant) as well as against contemporary variants of concern. Assessment of nAb to these different strains is recommended to be performed on, at least, the samples of the Phase 3 trial, for which efficacy data against these variants are also available. The applicant is requested to present their plans as soon as possible (see list of recommendations).

In study VAC31518COV1001, a total of 377 and 403 subjects were randomised and vaccinated in Cohort 1a and Cohort 3 respectively. A total of 125 and of 584 were enrolled and vaccinated in study VAC31518COV1002 (Cohort 1) and study VAC31518COV2001. The treatment discontinuation rate was <4.0% (range: 0.8% to 3.7%) in any of the studies/cohorts. There were no major relevant differences in baseline or demographic characteristics between the vaccine groups, including placebo, in any of the studies/cohorts.

In study VAC31518COV3001, 43,783 subjects were vaccinated. For further information, see efficacy section.

The submitted interim report of study VAC31518COV1001 contains immunology data through Day 85 (post-dose 1 and post-dose 2 data) for all participants in Cohorts 1 (aged ≥18 to ≤55 years) and through Day 57 for participants in Cohort 3 (aged ≥65 years, no data post-dose 2). Of note, for Cohort 3, the actual timing of the Day 57 blood draw ranged from 86 to 107 days post vaccination due to study pause (median visit = Day 87). For studies VAC31518COV1002, VAC31518COV2001, and VAC31518COV3001, the submitted interim reports contain available immunogenicity data collected through 28 days post-dose 1.

Selection of the dose, meeting pre-specified criteria, was based on immunogenicity (nAb response rate and Th1/Th2 ratio) and safety data up to 28 days post-dose 1 immunogenicity from Cohort 1a and available data from Cohort 3 of study VAC31518COV1001. Subsequent trials VAC31518COV1002 and VAC31518COV2001 have also evaluated two dose levels of 5×10^{10} vp and 1×10^{11} vp.

In trial VAC31518COV1001, neutralising antibody response rates were high for both dose levels (5×10^{10} vp and 1×10^{11} vp) and overall comparable between age categories (younger and the older adults >65 years of age) at 28 days post-first vaccination. A trend for higher GMT with the higher vaccine dose was observed in the young adults enrolled in the Phase 1 study conducted in Japan. This might however be explained by different factors, such as the higher proportion of females and of seropositive subjects at baseline in the 1×10^{11} vp when compared to the 5×10^{10} vp. In addition, the sample size was limited. Of note, similar nAb GMTs were observed between both dose levels in study VAC31518COV2001. Although not taken into account for dose selection, it should be noted that a trend for higher binding antibody GMT with the higher vaccine dose was observed at Day 29 and Day 85 in the younger adults and at Day 87 in the older adults. S specific - CD4 Th1 cells, as defined by the

applicant, were detectable at Day 15 and proportions of positive samples and median responses remained stable up to Day 29. CD8 Th1 cells were also detected as early as Day 15 and their proportions and median responses further increased by Day 29. Specific CD4 and CD8 T cell responses were overall in the same range for both dose levels, for both the proportion of positive samples and median responses. A low proportion of specific CD4 Th2 cells was detected in 1 subject only following vaccination. Th1/Th2 ratios were therefore ≥ 1 for all subjects. ELISpot results confirmed the results observed by the ICS method, an induction of Th1 cells responses in most of the vaccinated subjects, and overall comparable between groups. In conclusion, both dose levels, in both age groups, met the pre-specified criteria for dose selection, i.e. a lower limit of 95% confidence interval (CI) ≥65% and a Th1>Th2 within responder population. The lower limit of 95% confidence interval (CI) ≥65% was also observed in the 2 other studies for both dose levels. Taking all the above results into account, the applicant decided to continue the clinical development with the $5x10^{10}$ vp dose level.

Since the pre-specified criteria were met for both dose levels after one single vaccine dose, the applicant selected the single regimen to be tested in the VAC31518COV3001 trial. The persistence of humoral immune responses is not known for more than 3 months.

The second vaccine dose induced an increase in antibody titers, supporting the 2-dose schedule. Due to a study pause, immunogenicity evaluation of the added value of a second vaccine dose, with the adequate planned interval, will be missing for the older aged group. A 2-dose regimen is being evaluated in study VAC31518COV3009 as this may result in higher and more durable protective immune response.

The immune responses induced by the selected dose level and schedule ($5x10^{10}$ vp single dose) showed that:

Both specific binding antibodies and neutralising antibodies (nAb) were detectable 14 days following vaccination (study VAC31518COV1001 and study VAC31518COV2001). Both responder rates and Ab GMTs further increased up to 28 days post-vaccination in the older adults, whereas in the younger adults, Ab GMTs increase from 28 days up to 56 days post-vaccination. Ab titers then plateau up to 84 days post-vaccination (study VAC31518COV1001). Responder rates were already high at 28 days post-vaccination, so no/slight further increase were noted thereafter. No longer term data are available. Neutralising Ab titers correlated highly with binding Ab titers, in both the young and older adults, at both Day 29 and Day 71 (young adults only). This was performed with qualified, non-validated assays, and should be confirmed on samples from the Phase 3 trial, including participants of various countries and with comorbidities (see list of recommendations). In trial VAC31518COV3001, binding antibodies were detected, and GMTs were overall comparable between sites and countries, i.e. Brazil, South Africa and the US. Although results should be interpreted with caution due to the limited sample size per site, these results suggest that the population characteristics and environmental factors do not interfere with binding Ab responses induced by the vaccine.

- Functional antibodies, other than nAb, with a suggested role in viral clearance in vivo, were detected at 14 days post-vaccination and proportion and median of response increase up to Day 29 (no data available after Day 29), in both the younger and the older adults. High correlations were observed between the phagocytic score and nAb or binding Ab titers.
- Specific CD4 and CD8 Th1 cells were also detected at 14 days following vaccination. The proportion of CD4 Th1 positive samples remains stable (young adults) or slightly increases (older adults) up to 28 days post-vaccination, whereas the proportion of CD8 Th1 positive samples further increases up to 28 days post-vaccination. Medians of responses were apparently calculated taking into account all the samples, regardless of their positivity. Determination of medians of responses based on positive samples only would have given a better idea of the magnitude of the response in 'responder' subjects. The MAH is requested to

provide median of responses based on positive samples only and comparison between group in the final CSR (see list of recommendations).

- Median CD4 Th2 responses were overall undetectable at Day 15 and Day 29 in all vaccine groups. CD8 Th2 cells were not assessed.
- In addition to the characterisation by ICS, Th1 and Th2 phenotypes were characterised by IFN-γ and IL-4 ELISpot and results were consistent with those observed by the ICS method.
- Neutralising activity of immune sera from participants of study VAC31518COV1001 vaccinated with Ad26.COV2.S was tested against the emerging Kent variant, SARS-CoV-2 B.1.1.7 lineage. The capacity of the vaccine-induced nAb to neutralise the B.1.1.7 strain increased from Day 29 to Day 71. Further evolution over time is unknown. In addition, although a second vaccine-dose was demonstrated to boost the nAb response, the neutralising capacity for the Victoria 1/2020 strain remained higher compared to the B.1.1.7 strain. This difference in neutralisation capacity is not unexpected since the mutation N501Y is in the receptor binding domain of the Spike protein. A difference in neutralising capacity was also observed for the ChAdOx1 nCoV-19 vaccine. These data are preliminary and should be interpreted with caution as the assays have not been validated for direct comparisons across variants. Furthermore, the correlation between VNA titers and vaccine efficacy has not been established. The clinical relevance of the finding is unknown. Additional data on cross-neutralisation for clinically relevant and emerging SARS-CoV-2 strains by testing sera of human clinical participants, particularly of study VAC31518COV3001 in functional in vitro assays, are expected (see list of recommendations).

Immune responses induced by alternative dose levels were investigated in the Phase 2 VAC31518COV2001 trial, at dose level of $1.25x10^{10}$ vp, $2.5x10^{10}$ vp, $5x10^{10}$ vp, and $1x10^{11}$ vp. At 2 weeks and one-month post-vaccination, responder rates were high and comparable between the dose levels of $2.5x10^{10}$ vp, $5x10^{10}$ vp, and $1x10^{11}$ vp. The responder rates were lower for the $1.25x10^{10}$ vp vaccine group when compared to the 3 other groups. nAb GMTs were overall comparable between the $2.5x10^{10}$ vp, $5x10^{10}$ vp and $1x10^{11}$ vp groups 2 weeks following vaccination, with only a modest increase with dose levels. At Day 29, GMTs were increased when compared to 14 days post-vaccination. Lower nAb GMTs were also observed in the $1.25x10^{10}$ vp group at both timepoint when compared to the 3 other groups. At 28 days post-vaccination, nAb titers were overall comparable between younger and older adults in study VAC31518COV1001. In contrast to results of Cohort 1a (young adults), a trend for lower Ab GMT value was observed at 86 days post-vaccination. As consequence, GMT value was lower than the ones observed in the younger adults at 56- or 70-days post-vaccination. These decrease in neutralising titers maybe due to the immunosenescence phenomenon. As no subject > 75 years of age were included in the wtVNA analysis, Ab neutralising capacity is unknow for old subjects (> 75 years of age) but could be even more impaired.

A decrease in functionality of vaccine-induced Ab was also evidenced by the lower phagocytic score GMs and positivity rates observed 28 days post-vaccination in the older vs the younger adults. Binding Ab GMT values were lower in the older adults than those observed in the younger adults up to 3 months post-first vaccination, but differently than what it was observed for older adults in nAb titers, S-binding GMTs continued to increase until the last day that was registered. The proportion of positive samples in the older adults, for both CD4 and CD8 Th1 response, were lower than those observed in the younger adults. Median of the CD4 Th1 responses are comparable between both age groups, but median CD8 Th1 response was lower for the older when compared to the younger adults. However, these results cannot be interpreted since they are based on the total subjects and not on seropositive subjects.

Based on preliminary results, vaccine-induced immune responses appear to be lower in the older vs the younger adults. A decrease in functionality is observed, which is not unexpected since it is

recognised that older individuals might have impaired immune responses. The impact on the persistence and on the protection is unknown. These observations support studying the role of a second dose as it is currently being done with the ongoing trial (VAC31518COV3009).

Limited results showed that vaccine elicited immune responses in seropositive subjects were similar or higher and with the same kinetics when compared to seronegative subjects. A trend for higher nAb and binding Ab responses in females compared to males was observed, in both study VAC31518COV1001 and study VAC31518COV2001. No data available comparing immunogenic induced by vaccination in subjects with or without comorbidities.

Ad26 nAb were measured, at baseline and/or post-first vaccination, in studies VAC31518COV1001, VAC31518COV1002 and VAC31518COV3001.

Detectable baseline levels of Ad26 nAb were observed in only few participants in studies VAC31518COV1001 and VAC31518COV1002. In study VAC31518COV3001, vaccinated participants from Brazil had an overall Ad26 seroprevalence of 32.5% whereas seroprevalence in the US participants was 2.0% in the vaccine group. Although the responder rate (as measured by S-ELISA at Day 29) was slightly higher for Brazilian participants with no detectable Ad26 nAb at baseline when compared to Brazilian participants with detectable Ad26 nAb at baseline, no strong correlation was observed between S binding Ab levels 28 days post-vaccination and pre-existing Ad26 nAb at baseline. This is consistent with the overall comparable GMT values observed 28 days post-vaccination between the US site and the Brazilian sites.

Although Ad26-nAb were detected in more than 95% of participants following vaccination with Ad26.COV2.S in study VAC31518COV1001, it did not suggest an apparent negative impact of anti-Ad26 vector immunity induced by the first vaccine dose on the post-dose 2 insert specific vaccine-elicited humoral immune responses. Correlation between Ad26 nAb pre-dose 2 and SARS-CoV-2 nAb post-dose 2 was poor. The impact on binding Ab and T cell responses was not presented. Overall, the potential impact of natural or vaccine induced anti-Ad26 immunity on immunogenicity and vaccine efficacy remains unclear and should be further documented. Integrated results of the different trials included in the COVID-19 clinical development programme, and overall for Ad26-based vaccination, if possible, are further expected (see list of recommendations).

Results of studies VAC31518COV1001, VAC31518COV1002, and VAC31518COV2001 do not suggest an impact of the use of antipyretics/analgesics post-vaccination on the vaccine-induced nAb. Humoral vaccine-induced immune responses are available up to 85 days post-dose 1 for a limited number of young participants of study VAC31518COV1001. Ab responses were sustained up to 3 months post-vaccination. The persistence of the response for a longer period is unknown. In studies VAC31518COV1001, VAC31518COV1002 and VAC31518COV2001, participants are to be followed up to 1 year post last vaccination. Participants of the immunogenicity subset of study VAC31518COV3001 will be followed-up until 2 years. A longer follow-up for participants of Cohorts 1 and 3 of study VAC31518COV1001 would have allowed a direct comparison of the long-term immunogenicity for the 1- and 2-dose schedules. Participants of Cohorts 2a and 2b of study VAC31518COV1001 will be followed for a longer duration (36 and 38 months, respectively). The effect of a booster dose given at various timepoints will be evaluated in a 1- or 2-dose regimen in Cohorts 2a and 2b. In the absence of ICP, the timing for a booster dose will be difficult to establish. Nevertheless, the magnitude of the immune response, at various timepoints, following a boost is important to evaluate. In addition, because of the circulation of different strains, it is not known if such booster, i.e. with the prototype vaccine, will be needed in the future or if a new vaccine construct with a different or additional strain(s) would be needed. The expected data might nevertheless give an idea on the optimal/best timing for a boost, in term of immunogenicity, that could guide the choice for a boost timing, regardless of the strain(s) included in the vaccine. The assessment of the anamnestic response of

study VAC31518COV2001 would also give information on the need for a boost. However, the interval between vaccination and the assessment of an anamnestic response is 4 or 6 months, which may be too short (see list of recommendations) .

2.4.5. Conclusions on clinical pharmacology

Interim immunogenicity results are available from 4 ongoing trials. Results consistently demonstrated that a single dose of Ad26.COV2.S, at the selected dose level of 5x1010 vp elicits both humoral and cellular immune responses in adult ≥18 to ≤55 years and ≥65 years of age. However, vaccine-induced immune responses appear to be lower in the older vs the younger adults.

Neutralising and binding Ab were sustained up to 3 months after vaccination, in adults ≥18 to ≤55 years. Persistence of Ab over a longer period is not known. It is not known if Ab will persist in a similar fashion in older adults.

A 2.5-3 fold increase in antibody titers is observed following a second vaccine dose given at 56 days interval. This supports the applicant's choice to evaluate a 2-dose regimen in an efficacy trial.

The impact of pre-existing immunity to Ad26 still remains to be further investigated. First results of the COVID-19 program do not indicate a major impact of presence of Ad26-nAb on the vaccine-induced humoral response.

Preliminary data showed that neutralising antibodies elicited by Ad26.COV2.S were able to neutralise the B.1.1.7 lineage variant in vitro, although less efficiently than the reference strain. These data are however to be interpreted with caution as the assays have not been validated for direct comparison across variants.

In the absence of immunological correlates of protection, the clinical relevance of these findings is unknown.

2.5. Clinical efficacy

The applicant is performing two phase III studies. Both are multicentre, randomised, double blind, placebo-controlled studies, to determine pivotal efficacy and safety in adults aged 18 years and older. The efficacy, safety and immunogenicity of Ad26.COV2.S will be evaluated in these participants after one (VAC31518COV3001- ESEMBLE) or two intramuscular doses (VAC31518COV3009 - HORIZON).

The study VAC31518COV3001 is being carried out in several centres in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and US, and it will include up to 40,000 healthy adults aged 18 years and older. This study is the one presented by the applicant for this MAA.

The study VAC31518COV3009 is being carried out in several centres in US, UK, France, Germany, Italy, Spain, and South Africa and it will include up to 30.000 healthy adults aged 18 years. The applicant has not presented results from this study for the current MAA.

2.5.1. Dose response study(ies)

See section 2.4.3.

2.5.2. Main study(ies)

Title of study

Study VAC31518COV3001: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older.

Methods

Study participants

All participants must comply the following inclusion/exclusion criteria.

Inclusion criteria:

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Participants must provide consent.

2. Participant is willing and able to adhere to the prohibitions and restrictions specified in the protocol.

3. Age:

-Stages 1a and 1b: Participant is ≥18 to <60 years of age on the day of signing the ICF.

-Stages 2a and 2b: Participant is ≥60 years of age on the day of signing the ICF.

4. Medical conditions:

Stages 1a and 2a: In the investigator's clinical judgement, participant must be either in good or stable health, including a BMI <30 kg/m2. Participants may have underlying illnesses not associated with increased risk of progression to severe COVID-19 (per US CDC), as long as their symptoms and signs are stable and well-controlled.

Stages 1b and 2b: In the investigator's clinical judgement, participant may have a stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19.

5. Participants must be either: a. Not of childbearing potential; b. Of childbearing potential and practicing an acceptable effective method of contraception and agrees to remain on such a method of contraception from providing consent until 3 months after administration of study vaccine.

6. All participants of childbearing potential must have a negative highly sensitive urine pregnancy test at screening and have a negative highly sensitive urine pregnancy test on the day of and prior to study vaccine administration.

7. Participant agrees to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving the study vaccine.

8. Must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

9. Must be able to read, understand, and complete questionnaires in the eCOA (ie, the COVID-19 signs and symptoms surveillance question, the e-Diary, and the electronic patient-reported outcomes (ePROs).

Exclusion criteria:

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Participant has a clinically significant acute illness (this does not include minor illnesses such as diarrhoea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned study vaccination.

2. Participant has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine).

3. Participant has abnormal function of the immune system resulting from:

   a. Clinical conditions (e.g., autoimmune disease or potential immune mediated disease or known or suspected immunodeficiency, or participant on hemodialysis) expected to have an impact on the immune response of the study vaccine. Participants with clinical conditions stable under non-immunomodulator treatment (e.g., autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator. Non-immunomodulator treatment is allowed as well as steroids at a non-immunosuppressive dose or route of administration.

   b. Chronic or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent.
   Note: Ocular, topical or inhaled steroids are allowed.

   c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of study vaccine and during the study.

4. Participant received treatment with Ig in the 3 months or exogenous blood products (autologous blood transfusions are not exclusionary) in the 4 months before the planned administration of the study vaccine or has any plans to receive such treatment during the study.

5. Participant received or plans to receive: a. Licensed live attenuated vaccines - within 28 days before or after planned administration of study vaccine; b. Other licensed (not live) vaccines - within 14 days before or after planned administration of study vaccine.

6. Participant previously received a coronavirus vaccine.

7. Participant received an investigational drug within 30 days or used an invasive investigational medical device within 30 days or received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study.

8. Participant is pregnant or planning to become pregnant within 3 months after study vaccine administration.

9. Participant has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the wellbeing) or that could prevent, limit, or confound the protocol-specified assessments.

10. Participant has a contraindication to IM injections and blood draws, e.g., bleeding disorders.

11. Criterion deleted per Amendment 1.

12. Participant has had major psychiatric illness which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.

13. Participant cannot communicate reliably with the investigator.

14. Participant who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.

15. Stages 1a and 2a:

- Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19 (per US CDC), ie, participants with moderate to severe asthma; chronic lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension; moderate to severe high blood pressure; obesity (body mass index [BMI] ≥30 kg/m2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; and sleep apnea.

- Participants with a history of or current Parkinson's disease; seizures; ischemic strokes; intracranial hemorrhage; encephalopathy and meningoencephalitis.

16. Stages 1a and 2a:

Participant has a history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence).

17. Participant has a history of acute polyneuropathy (e.g., Guillain-Barré syndrome).

18. Stages 1a and 2a: Participant had surgery requiring hospitalisation (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalisation, or has surgery requiring hospitalisation planned during the time the participant is expected to participate in the study or within 6 months after study vaccine administration.

19. Stages 1a and 2a: Participant has chronic active hepatitis B or hepatitis C infection per medical history.

Treatments

Ad26.COV2.S was supplied at a concentration of 1×10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp.

Placebo was supplied as 0.9% NaCl in single-use vials, with an extractable volume of 0.5 mL.

For blinding purposes, all participants receive Ad26.COV2.S or placebo using the same volume (ie, 0.5 mL).

Study vaccine was administered by IM injection into the deltoid muscle, preferably of the non-dominant arm. If an injection cannot be given in the deltoids due to a medical or other contraindication, use alternative locations such as the hip, thigh or buttocks was allowed.

Objectives and outcomes/endpoints

The objectives and outcomes/endpoints are shown in the following table.

Objectives	Endpoints
Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19, as compared to placebo, in SARS-CoV-2 seronegative adults.	• First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)
Secondary	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, severe/critical COVID-19, as compared to placebo.	• First occurrence of molecularly confirmed, severe/critical COVID-19, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19, as compared to placebo, in adults regardless of their serostatus.	• First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset 1 day post-vaccination • First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed moderate to severe/critical COVID-19 as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed, moderate to severe/critical COVID-19 with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo.	• First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalisation, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) and linked to any molecularly confirmed, COVID-19 at least 14 days post-vaccination (Day 15)

	• First occurrence of COVID-19 requiring medical intervention and linked to any molecularly Confirmed, COVID-19 at least 14 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on SARS-CoV- 2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe/critical COVID-19	Assessment of the SARS-CoV-2 viral load by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR), in participants with molecularly confirmed, moderate to severe/critical COVID-19 by serial viral load measurements during the course of a COVID-19 episode.
To assess the effect of Ad26.COV2.S on molecularly confirmed mild COVID-19	• First occurrence of molecularly confirmed, mild COVID-19, at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, mild COVID-19, at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on COVID- 19 as defined by the US FDA harmonized case definition	• First occurrence of molecularly confirmed COVID-19 at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed COVID-19 at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on all, molecularly confirmed symptomatic COVID-19, as compared to placebo	• Burden of disease (BOD) endpoint derived from the first occurrence of molecularly confirmed symptomatic COVID-19 (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 14 days post-vaccination (Day 15) • BOD endpoint derived from the first occurrence of molecularly confirmed symptomatic COVID-19 (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 28days post- vaccination (Day 29).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination, using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) with onset at least 28 days after vaccination (Day 29)
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	• Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA
Exploratory	
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or	Serologic conversion between baseline (Day 1; pre-vaccination) and Day 29 post-vaccination using an ELISA

undetected infections with SARS-CoV-2, as compared to placebo from Day 1 to Day 29	and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral RNA load compared to placebo for mild COVID-19	Assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed, mild COVID-19 by serial viral load measurements during the course of a COVID-19 episode
To assess the effect of Ad26.COV2.S on health care utilisation (such as hospitalisation, ICU admission, ventilator use) linked to any molecularly confirmed COVID-19, as compared to placebo	Health care utilisation (such as hospitalisation, ICU admission, ventilator use) linked to any molecularly confirmed COVID-19 at least 14 days post-vaccination (Day 15) • Health care utilisation (such as hospitalisation, ICU admission, ventilator use) linked to any molecularly confirmed COVID-19 at least 28 days post-vaccination (Day 29)
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection in participants with comorbidities associated with increased risk of progression to severe COVID-19, as compared to placebo	First occurrence of SARS-COV-2 infection (serologically and/or molecularly confirmed) in participants with comorbidities associated with increased risk of progression to severe COVID-19 with onset at least 28 days after vaccination (Day 29)
To explore the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not previously described, as compared to placebo	• First occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days after vaccination (Day 15) • First occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 28 days after vaccination (Day 29)
To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo	•Deaths occurring at least 14 days after vaccination (Day 15) •Deaths occurring at least 28 days after vaccination (Day 29)
To evaluate the immune response in participants with COVID-19 in relation to risk of development of COVID-19, protection induced by Ad26.COV2.S, and risk of accelerated disease	Assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), with the risk of COVID-19 and protection induced by the study vaccine
In a subset of participants to further assess the humoral immune response to Ad26.COV2.S, as compared to placebo	Humoral immunogenicity endpoints: – Functional and molecular antibody characterisation including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire – Adenovirus neutralisation as measured by VNA – Analysis of antibodies to S and the receptor- binding domain (RBD) of the SARS-CoV-2 S protein

	– SARS-CoV-2 neutralisation as measured by virus neutralisation assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein)
To explore changes in the SARS-CoV-2 genome	Development of SARS-CoV-2 variants
To evaluate patient-reported outcomes (PROs) in relation to the presence of SARS-CoV-2 infection and the presence, severity and duration of COVID- 19 signs and symptoms in participants who received Ad26.COV2.S, as compared to placebo	- Presence, severity and duration of COVID-19 signs and Symptoms; - Confirmation of SARS-CoV-2 infection by molecular testing
To assess the difference in severity of cases in participants who received Ad26.COV2.S as compared to placebo	Reduction in severity of COVID-19 signs and Symptoms
To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS- CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity	Analysis of antibodies binding to coronaviruses other than SARS-CoV-2 by ELISA
To assess the incidence of co-infection of COVID- 19 and other respiratory pathogens and to assess the effect of the vaccine during such co-infections as well as to estimate the incidence of other respiratory pathogens during the study period.	Analysis of broad respiratory pathogens panel in the nasal swabs collected during a confirmed COVID-19 episode and in a subset of nasal swab samples from participants with a symptomatic infection.
To examine the degree of frailty in terms of balance in participants receiving Ad26.COV2.S vs placebo, the effect of degree of frailty on vaccine efficacy, and the degree of frailty in cases occurring in the Ad26.COV2.S vs placebo group.	Utilisation of the frailty index as a measure of frailty prior to vaccination comparing the Ad26.COV2.S vs placebo group and as a measure to compare cases in the Ad26.COV2.S vaccine vs placebo group.

Notes to the previous table:

- Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result by a central laboratory using a PCR-based or other molecular diagnostic test.

- All efficacy analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated in the statistical analysis plan (SAP).

Efficacy assessments and procedures:

An active surveillance of COVID-19 signs and symptoms is in place for all participants. This surveillance (symptom check) is done through a digital tool referred to as 'electronic clinical outcome assessment' (eCOA). Participants are asked at least twice a week, through this eCOA, if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. Participant failing to complete the surveillance question upon reminders were contacted by the site.

The criteria for suspected COVID-19 (ie, the triggers to proceed with home-collection of the nasal swabs on COVID-19 Day 1-2 and to proceed with the COVID-19 Day 3-5 visit) were prespecified as follows: a positive RT-PCR result for SARS-CoV-2, through a private or public laboratory independent of the study, whether symptomatic or asymptomatic OR new onset or worsening of any 1 of the

symptoms from a pre-defined list of symptoms (symptoms from the CDC list and additional symptoms), which lasts for at least 24 hours, not otherwise explained.

In the event a participant experiences COVID-19-like signs and symptoms meeting pre-specified criteria for suspected COVID-19, or a participant became aware of a positive RT-PCR test result for SARS-CoV-2 outside the study site context, this triggered swabbing and other specific procedures. The site had to reach out to the participant at the latest on COVID-19 Day 2 to assess whether the reported signs and symptoms qualified as a suspected COVID-19 episode using prespecified criteria. As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement was used to exclude vaccine-related events when assessing suspected COVID-19.

Case Definitions

Case Definition for Moderate COVID-19

• A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g. nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample

AND at any time during the course of observation:

Any 1 of the following new or worsening signs or symptoms:	**OR**	**Any 2 of the following new or worsening signs or symptoms:**
Respiratory rate ≥20 breaths/minute		Fever (≥38.0°C or ≥100.4°F)
Abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level*		Heart rate ≥90 beats/minute
Clinical or radiologic evidence of pneumonia		Shaking chills or rigors
Radiologic evidence of deep vein thrombosis (DVT)		Sore throat
Shortness of breath or difficulty		Malaise as evidenced by 1 or more of the following**: - Loss of appetite - Generally unwell - Fatigue - Physical weakness
		Headache
		Muscle pain (myalgia)
		Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)**
		New or changing olfactory or taste disorders
		Red or bruised looking feet or toes

* SpO2 criteria were adjusted according to altitude per the investigator judgement.

** Having 2 or more elements of a symptom (e.g., vomiting and diarrhoea or fatigue and loss of appetite) was counted only as 1 symptom for the case definition. To meet the case definition, a participant had to have at least 2 different symptoms.

Case Definition for Severe/Critical COVID-19

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g. nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample.

AND any 1 of the following at any time during the course of observation:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level*, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg).

* SpO2 criteria will be adjusted according to altitude per the investigator judgement.

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]).

- Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors).

- Significant acute renal, hepatic, or neurologic dysfunction.

- Admission to the ICU.

- Death.

Clinical Severity Adjudication Committee:

All cases meeting the severe/critical criteria are adjudicated by the Clinical Severity Adjudication Committee (CSAC) to determine if the case is severe/critical in their judgement.

All potential severe/critical COVID-19 cases defined as those cases that meet the severe/critical definition by scoring of signs and/or symptoms or meet the moderate endpoint definition with a total of 3 or more signs and/or symptoms were assessed independently by the CSAC.

Classification of severity was based on the highest degree of severity during the observation period. Classification of a case as severe/critical by the CSAC is considered definitive. The CSAC independently evaluates the severity of the COVID-19 cases in a blinded manner.

Additional information was provided in the Clinical Severity Adjudication Committee Charter.

Case Definition for Mild COVID-19

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g. nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample;

AND at any time during the course of observation:

- One of the following symptoms: fever (≥38.0°C or ≥100.4°F), sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, muscle pain (myalgia), gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, new or changing olfactory or taste disorders, red or bruised looking feet or toes, or shaking chills or rigors.

A case is considered mild when it meets the above case definition but not the moderate to severe/critical definition.

US FDA Harmonized Case Definition for COVID-19

If a participant presents with symptoms as those listed by the US FDA harmonized case definition (Center for Disease Control and Prevention. Symptoms of Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html., see picture below), the investigator (or designated medically trained clinician) should assess if these are suggestive of COVID-19:

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g. nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample; AND

- COVID-19 symptoms consistent with those defined by the US FDA harmonized case definition at the time of finalisation of this protocol: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea.

BOD endpoint

To evaluate the effect of the vaccine against symptomatic molecularly confirmed COVID-19, including mild infections, a BOD endpoint was evaluated based on the first occurrence of molecularly confirmed COVID-19, including mild, moderate and severe/critical case definitions, with onset at least 14 days after vaccination (Day 15) and with onset at least 28 days after vaccination (Day 29). In this study, the BOD endpoint is defined as taking the value 1 for mild and moderate disease and the value 2 for severe disease (implicitly assigning a value of 0 for no disease [not infected or asymptomatic infection]).

Case Definition for Asymptomatic or Undetected COVID-19

If a participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms.

AND

- has a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g. nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample

OR

- develops a positive serology (non-S protein) test

Then, the participant is considered to have experienced asymptomatic or undetected COVID-19.

SARS-CoV-2 Seroconversion Assessment:

An immunologic test for SARS-CoV-2 seroconversion (ELISA and/or SARS-CoV-2 immunoglobulin assay) based on SARS-CoV-2 N protein will be performed to identify cases of asymptomatic infection on samples obtained at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination.

Virology assessments:

Participants with suspected COVID-19 self-collected a nasal swab at home on the Day of symptom's onset or the following day (Day 1-2). Another nasal swab was taken on Day 3-5 by a health care professional during site visit. The nasal swabs could also be collected at hospital or other location, if needed. Nasal swabs were then self-collected once every 2 days (by the participant at home). Saliva samples were collected by the participant on COVID-19 Day 3-5 and then once every 2 days if

participants met the protocol prespecified criteria for suspected COVID-19 on COVID-19 Day 1-2 and COVID-19 Day 3-5 (as assessed during Part 1 of the COVID-19 Day 3-5 visit). Nasal samples were collected with a foam tip mid-turbinate swab. The saliva samples were collected with the OMNIgeneOral RNA/DNA device.

Virological confirmation of the endpoint cases and viral shedding assessment:

Nasal swabs were used to detect and/or quantify SARS-CoV-2. Exploratory quantification of the SARS-CoV-2 viral load in saliva samples could also be performed. Nasal swabs were tested at the central laboratory. All nasal swabs were also tested by a local laboratory for case management, as central laboratory results are not be available in real time. In case a SARS-CoV-2 local RT-PCR test is not available, the RT-PCR on swab sample will be performed centrally. Sites have to use a molecular (PCR) diagnostic test from Tier-1 and Tier-2 list of assays, all with FDA EUA, as predefined by the COVID-19 vaccine taskforce (formerly operation warp speed). Confirmation testing was done by a central lab at Washington University, using the Tier-1 Abbott Realtime SARS-CoV-2 RT-PCR assay. The Abbott m2000 qualitative PCR received EUA and uses a dual target strategy to detect stretches in the RdRp and in the N genes. An unrelated RNA sequence is spiked as internal processing control. All sites in South Africa used BARC as local central lab for testing.

Gene sequencing:

Sequencing of all cases samples is ongoing, in order to detect which are the infectious strains, particularly in South Africa and Brazil because of the circulation of variants of concern during the study period. Nasal swab specimens from SARS-CoV-2 RT-PCR confirmed cases were used for sequence analysis. One sample per subject, taken as close as possible to the onset of symptoms, was selected when SARS-CoV-2 viral load was >200 copies/mL. Next-generation sequencing was performed using the Swift Biosciences SNAP Version 2.0, performed at the Virology Laboratory of the University of Washington. The SARS-CoV-2 Wuhan-Hu1 variant including the D614G mutation is taken as the reference sequence. Only S gene information was considered, and whole viral genome sequences have not yet been analysed.

Efficacy evaluations

Sample size

The sample size has been triggered by the total number of cases TNE. The assumptions were VE of 60%, Null VE value of 30%, randomisation ratio of 1:1, one-sided 2.5% alpha and 90% statistical power employing the sequential probability ratio test [SPRT] to perform a fully sequential design analysis. That lead to a target number of events (TNE) of 154.

The applicant performed a relevant change in the third protocol amendment and the total sample size was decreased from 60,000 participants to 40,000. The applicant's rationale was based in that the COVID incidence was underestimated at the moment of the trial design, and that the attack rates were actually higher. Thus, statistical calculations supported the decision to randomise 40.000 patients to obtain a minimum TNE of 154.

Randomisation

Central randomisation was implemented in this study. Participants were randomly assigned to 1 of 2 vaccination groups (active vaccine [Group 1] versus placebo [Group 2]). This was based on a computer-generated randomisation schedule. The randomisation was balanced by using randomly

permuted blocks and was stratified by vaccination unit, age group, and absence/presence of comorbidities that are or might be associated with an increased risk of progression to severe COVID-19.

The randomisation system was used to control the age distribution of participants in the trial; in particular the age ranges of ≥18 to <40 and ≥40 to <60 years can be closed separately for further randomisation in order to obtain a distribution of approximately 20% and 50% for these age ranges, respectively, and to have a minimum of approximately 30% of the population to be ≥60 years.

Blinding (masking)

Blinding will be guaranteed by the preparation of the study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation and dispensing, and by the administration of vaccine in a masked syringe by a blinded study vaccine administrator.

Data that may potentially unblind the study vaccine assignment (i.e. immunogenicity data, study vaccine accountability data, study vaccine allocation, biomarker, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimised. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Investigators may receive requests to unblind study participants who become eligible to receive an authorised/licensed COVID-19 vaccine if/when these become available. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorised/licensed vaccine according to local immunisation guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures as described in the protocol.

Statistical methods

Overall statistical design

This is a fully sequential trial in which the statistical boundaries were based on a truncated sequential probability ratio test (SPRT). Two co-primary endpoints were predefined based on the case definition with onset of at least 14- and 28-days post-vaccination, in the *per protocol* population set at an overall 2.5% one-sided alpha level.

The trial positiveness was predefined for a simultaneously superiority for the two-coprimary endpoints against the null value of 30% VE, with both point estimates >50% VE, and ≥5 cases in the placebo arm.

Vaccine Efficacy = 100 x (1-ratio of incidence vaccine/placebo)%

The statistical monitoring for efficacy started once:

- the following criteria were met for cases of onset at least 28 days after vaccination: (a) ≥6 cases for the ≥60years age, (b) ≥42 cases moderate to severe/critical, (c) ≥5 cases severe/critical, and assessed weekly

AND

- pre-specified non-efficacy boundaries were met OR 154 cases with onset 28 days after vaccination

Also, the analysis might be triggered in case non-efficacy boundary was met OR the harm boundary was crossed.

Multiplicity for secondary endpoints

The evaluation of secondary endpoints was adjusted for multiple testing of multiple endpoints (using a graphical approach, Bretz et al 2009) and potential stopping at an interim analysis evaluation through a Pocock boundary using Wang-Tsiatis with Delta=0.5. Since no interim analysis was performed, the statistical hypothesis testing scheme started at the primary analysis. The associated alpha levels and confirmatory endpoints are listed in the following Table. For all displays in the body of this report, an adjusted 95% CI is shown when a statistical hypothesis was evaluated to control the false positive rate. Otherwise data are summarised descriptively, using a 95% CI.

LEFPE02: Listing of Alpha Levels Used and Split at the Analysis Timepoints; Per Protocol Set (Study VAC31518COV3001)

Endpoint	Timing of the analysis	Total Number of cases	Number of cases in the vaccine group	Alpha level[1]	Information fraction
Primary endpoint with onset at least 14 days after vaccination[2]	Primary Analysis	464	116	0.05**	.
Primary endpoint with onset at least 28 days after vaccination[2]	Primary Analysis	259	66	0.05**	1.681818
All symptomatic infections (BOD) with onset at least 14 days after vaccination	Primary Analysis	468	117	0.05**	.
All symptomatic infections (BOD) with onset at least 28 days after vaccination	Primary Analysis	261	66	0.025000**	.
All severe cases with onset at least 14 days after vaccination	Primary Analysis	74	14	0.025000**	.
All severe cases with onset at least 28 days after vaccination	Primary Analysis	39	5	0.012500**	.
All cases requiring medical intervention with onset at least 14 days after vaccination	Primary Analysis	10	2	0.05	.
All cases requiring medical intervention with onset at least 28 days after vaccination	Primary Analysis	5	0	0.05	.
All other endpoints	Primary Analysis			0.05	

[1] Used for the calculation of the (adjusted) (1-Alpha)x100% confidence intervals.
[2] Same alpha used for non-confirmed cases.
The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions (** indicates adjusted).
[LEFPE02.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\LEFPE02.SAS] 23JAN2021, 09:45

Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

- Full Analysis Set (FAS): All randomised participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrolment. Analyses of safety will be performed on the FAS. Vaccine efficacy analyses can be repeated using the FAS.

- Per-protocol Efficacy (PP) population: Participants in the FAS who receive study vaccine and who are seronegative at the time of vaccination and who have no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine. The PA of VE will be based on the PP population. The PP will be the main analysis population for efficacy analyses.

The following variables are relevant for in/exclusion of analyses:

- If a participant is seropositive at baseline, the participant is excluded from the PP set. In case the test result is missing or unknown the participant is considered as seronegative for analysis purposes.

- PCR positive (PCR+) or negative (PCR-) at baseline: a sample for SARS-CoV-2 infection at baseline is collected for each participant. For participants with a positive SARS-CoV-2 infection during the study this sample is tested. If a participant was analysed PCR+ at baseline, the participant is excluded from the PP set.

Results

Participant flow

A total of 44,325 participants were randomised to the Ad26.COV2.S vaccine arm (n=22,174) or to the placebo arm (n=22,151) to the placebo arm. The proportion of subjects randomised and not vaccinated was very low and balanced between arms (1.3% vs 1.2% in the Ad26.COV2.S and placebo arms respectively). A total of 43,783 randomised participants received the study vaccine (21,895 and 21,888 in the Ad26.COV2.S vs placebo arms). This cohort constitutes the Full Analysis Set (FAS). Of the participants in the FAS, 19,630 (89.7%) and 19,691 (90.0%) were included in the Per Protocol Efficacy Set (PP), respectively in the Ad26.COV2.S vs placebo arms (total of 39,321).

A total of 4462 participants were eliminated from the PP. Baseline seropositivity for SARS-CoV-2 was the main reason for elimination from the PP set (n=4217) and/or being PCR positive at the time of vaccination the second reason (n=238). Other reasons were major protocol deviations (evaluated to possibly impact efficacy, on inclusion/exclusion criteria, or received wrong treatment, or received a disallowed concomitant medication). Reasons for elimination from the PP were balanced across groups.

In the FAS, 54.6% of participants had a follow-up of at least 2 months after vaccination (calculated as 8 weeks) in both arms (in the PP, respectively 54.6% and 54.7% Ad26.COV2.S vs placebo arms), at the time of this primary analysis. The median follow-up time after vaccination was 58.0 days in both arms, in both the FAS and the PP.

In the FAS, 1080 (4.9%) and 1177 (5.4%) participants were unblinded respectively in the vaccine and placebo arms, up to the cut-off date of 22 January 2021. The percentage of unblinding is balanced across arms. Unblinding were all due to request to be unblinded by participants who became eligible to receive an authorised/licensed COVID-19 vaccine (no unblinding for safety concern). Following emergency use authorisation of COVID-19 vaccines in December, participants were offered the possibility to have access to the vaccines if they were part of the risk groups for which the vaccine was recommended (it was essentially in the US). Participants that were unblinded for this purpose remained under follow up in the study. Data collected up to unblinding are included in the analysis described in this report.

Very few subjects terminated study participation prematurely at the time of data cut-off point for the primary analysis (in the FAS: 49 [0.2%] vs 96 [0.4%] and in the PP: 41 [0.2%] vs 89 [0.5%] in the Ad26.COV2.S vs placebo arms respectively). The main reason for termination was withdrawal by subject (in the FAS: 35 [0.2%] vs 66 [0.3%] and in the PP 30 [0.2%] vs 62 [0.3%] in the Ad26.COV2.S vs placebo arms respectively). The proportion of premature termination was slightly higher in the placebo vs vaccination arm.

Recruitment

Date study initiated: 21 September 2020 (Date first participant signed informed consent)

Date study completed: Not applicable, the study is ongoing.

Date of data cutoff: 22 January 2021 (Date of last observation recorded as part of the database for primary analysis).

Conduct of the study

There were 3 amendments to the protocol. The first amendment (15 September 2020) was adopted before any study-related procedures had begun and mainly implemented the selected dose level of 5×10^{10} vp for Ad26.COV2.S based on data from the FIH study VAC31518COV1001. The second amendment (29 October 2020) included the following changes: clarification that all participants that have an RT-PCR positive finding for SARS-CoV-2, even if asymptomatic, will be followed until there are 2 consecutive negative PCRs, correction of errors and minor editorial changes. The third amendment (14 December 2020) included the main following changes: The occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days postvaccination was added as a co-primary endpoint in addition to the current primary endpoint counting as of 14 days post-vaccination. The applicable secondary and exploratory endpoints were updated similarly to also include COVID-19 cases with onset at least 28 days post-vaccination. In addition, the total sample size was reduced from 60,000 to approximately 40,000 participants. The protocol is further amended to change the conditions for monitoring whether efficacy greater than 30% is achieved using the sequential monitoring algorithm. Furthermore, additional secondary and exploratory objectives and endpoints were added.

Baseline data

Demographic and Baseline Characteristics

FAS:

The main region was Northern America (United States: 44.1% of subjects in both groups), followed by Latin America (Brazil, Chile, Argentina, Colombia, Peru, Mexico: 40.9% of subjects in both groups). There was a substantial representation of Southern Africa (15.0% in both groups). Latin American subjects mainly originated from Brazil (16.6%) Colombia (9.7%) and Argentina (6.8%).

Approximately a fifth of the participants were frontline essential workers (6.9% vs. 7.0%) or health care professionals (13.0% vs. 12.8%). There were only few long-term care residents: 0.3% (n=63) vs. 0.4% (n=85) in respective groups.

A total of 9.6% of the participants were SARS-CoV-2 seropositive at baseline (9.8% vs 9.4% in respective arms). These participants were excluded from the PP set. Data on serostatus was missing in 637 vaccinees vs 625 placebo subjects. SARS-CoV-2 seroprevalence was highest in South Africa region (23.8% vs. 22.9%), followed by Latin America (10.6% vs. 10.0%), and Northern America (4.4% vs. 4.3%). Seroprevalence varied across countries from Latin America (for the most represented countries: Argentina: 6.1% vs. 5.6%, Brazil: 6.0% vs. 6.0%, Colombia: 12.4% vs. 11.4%).

In the FAS, mean age was 50.7 years (median 52.0 years) in both groups, with a range of 18;100 years and 18;94 years respectively in the Ad26.COV2.S group vs the placebo group. Of the FAS participants, 33.5% were ≥60 years in both groups (23.9% vs. 24.5% were 60-69 years, 8.6% vs. 8.1% were 70-79 years, 1.0% vs. 1.0% were ≥80 years in the Ad26.COV2.S group vs the placebo group). The proportion of participants ≥65 years was 19.5% (n=4259) and 19.7% (n=4302), and the proportion of participants ≥75 years was 3.7% (n=809) and 3.3% (n=732), respectively in the Ad26.COV2.S group vs the placebo group.

The proportion of females was 44.9% vs 45.2% in the vaccine vs the placebo arm.

Overweight (BMI 25 - <30 kg/m2) and obese (BMI ≥30 kg/m2) individuals were well represented in the trial, with 37.6% vs 38.6% of the participants being overweight, and 28.6% vs. 28.4% being obese in respective arms. At least one comorbidity was present at baseline for 40.8% of the participants in both groups (29.0% vs. 28.6% had one comorbidity, 8.7% vs. 8.9% had two

comorbidities, and 3.1% vs. 3.3% had 3 or more comorbidities). Obesity (28.7% vs. 28.4%) was the most represented comorbidity, followed by hypertension (10.2% vs. 10.5%) and type 2 diabetes mellitus (7.3% vs. 7.3%). Other comorbidities present in more than 1% of the subjects were: asthma, COPD, and serious heart conditions. Of the FAS, 2.7% vs 2.8% of the participants were HIV infected, in the vaccine vs the placebo arm. The HIV infection status is unknown for 59.2% in both arms. In the FAS, 0.2% of the subjects in both groups present an immunodeficiency condition (43 vs. 36 participants in respective groups), <0.1% present secondary immunodeficiency (7 vs. 3), 0.5% present malignant neoplasm (112 vs. 114), and 0.5% present chronic kidney disease (112 vs. 118) (Source: TSIMH01).

PP:

Participants who were SARS-CoV-2 seropositive at baseline were excluded from the PP set.

The main region was Northern America (United States: 46.8% and 46.6% in respective groups), followed by Latin America (Brazil, Chile, Argentina, Colombia, Peru, Mexico: 40.6% and 40.7% of subjects in respective groups). There was a substantial representation of Southern Africa (12.6% and 12.7% in respective groups). Latin American subjects mainly originated from Brazil (17.3%) Colombia 2125 (9.5%) and Argentina (7.2%).

Data on the profession of participants and the number of long-term care residents was not provided for the PP.

In the PP, mean age was 51.1 and 51.2 years in respective groups (median 52.0 years and 53.0 years respectively), with a range of 18;100 years and 18;94 years respectively in the Ad26.COV2.S group vs the placebo group. Of the PP participants, 34.6% were ≥60 years in both groups (24.6% vs. 25.1% were 60-69 years, 9.0% vs. 8.4% were 70-79 years, and 1.0% vs 1.0% were ≥80 years, in the Ad26.COV2.S group vs the placebo group).

The proportion of participants ≥65 years was 20.3% (n=3984) and 20.4% (n=4018), and the proportion of participants ≥75 years was 3.8% (n=755) and 3.5% (n=693), respectively in the Ad26.COV2.S group vs the placebo group.

The proportion of females was 44.3% vs 44.6% in the vaccine vs the placebo arm.

Overweight (BMI 25 - <30 kg/m2) and obese (BMI ≥30 kg/m2) individuals were well represented in the trial, with 38.1% vs 39.1% of the participants being overweight, and 27.6% vs. 27.5% being obese in respective arms. At least one comorbidity was present at baseline for 39.9% vs. 40.0% of the participants in respective groups (28.2% vs. 28.0% had one comorbidity, 8.5% vs. 8.8% had two comorbidities, and 3.1% vs. 3.2% had 3 or more comorbidities). Obesity (27.6% vs. 27.5%) was the most represented comorbidity, followed by hypertension (10.2% vs. 10.3%) and type 2 diabetes mellitus (7.2% vs. 7.2%). Other comorbidities present in more than 1% of the subjects were: asthma (1.3%), COPD (1.0%), and serious heart conditions (2.4%). Of the FAS, 2.4% vs 2.5% of the participants were HIV infected, in the vaccine vs the placebo arm.

PP within regions:

Age distribution was roughly similar between South African and Latin America regions, but mean/median age and the proportion of elderly subjects were higher in the US. The proportion of subjects ≥65 years is not presented for the PP. The most frequent comorbidities were the same across regions, although frequencies were slightly different. HIV infection was more frequent in South Africa.

Concomitant therapies

Antipyretics were recommended post-vaccination for symptom relief as needed. Prophylactic antipyretic use was not encouraged. Analgesics/antipyretics were used by 1,128 (5.2%) participants in

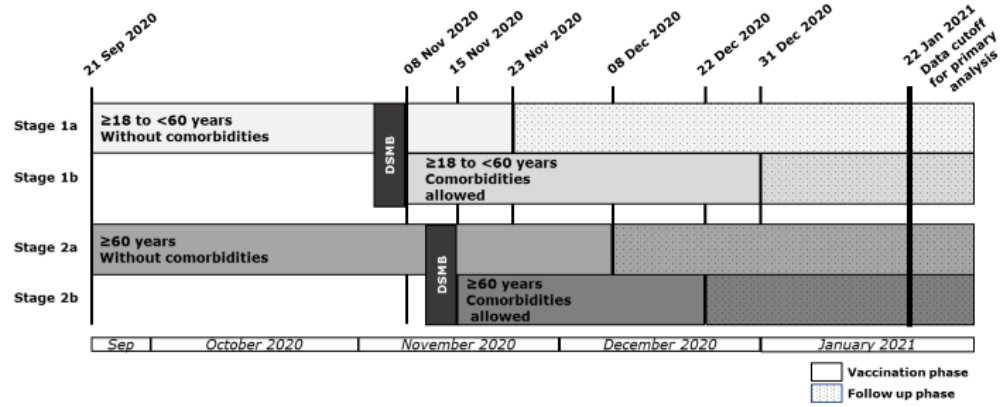
the Ad26.COV2.S group and 365 (1.7%) participants in the placebo group up to 7 days post-vaccination. The most frequently used analgesics/antipyretics were paracetamol, metamizole sodium, and ibuprofen with a frequency that was higher in participants in the Ad26.COV2.S group, compared to participants in the placebo group. Concomitant medications of special interest (i.e. analgesics/antipyretics and corticosteroids) were used by less than 6% of participants in both groups.

Numbers analysed

Refer to subject's participant flow.

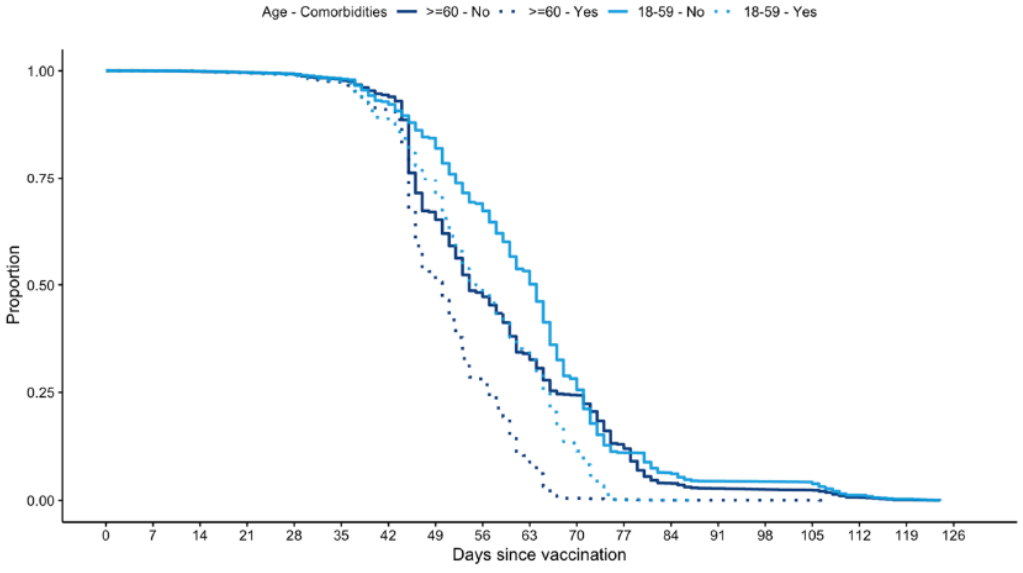
Extent of exposure

The study was staggered.



Note: planned sample size was overall 40,000 for the study and approximately 2000 subjects were enrolled in Stage 1a and 2a

Figure 10: Schematic overview of the enrolment across the study stages.



Solid dark blue line: ≥60 years of age without comorbidities
Dotted dark blue line: ≥60 years of age with comorbidities
Solid light blue line: ≥18 to <60 years of age without comorbidities
Dotted light blue line: ≥18 to <60 years of age with comorbidities

Adapted from GSIDS01

Figure 11: Kaplan-Meier Curves of Time on Study by Age and Comorbidities; Per Protocol Analysis Set (VAC31518COV3001)

Outcomes and estimation

Co-primary and key Secondary Vaccine Efficacy Results.

The summaries of VE against molecularly confirmed COVID-19 with onset 14 days and 28 days, and 1 day after vaccination are presented in the below tables.

Cases with an onset at least Day 14:

For the primary endpoint 'moderate to severe/critical COVID-19' with an onset beyond Day 14, there were 116 vs 348 cases in the vaccine vs the placebo group, corresponding to a 66.9% efficacy (Adjusted 95% CI: 59.03; 73.40). The lower limit (LL) of the CI of 59% was well above the pre-specified limit of 30%. Therefore the primary objective was met for this endpoint. It is noted that of the 116 vs. 348 cases with an onset beyond Day 14, 66 vs. 193 cases occurred beyond Day 28 (hence nearly half occurred in the period 15-28 days, i.e. 50 vs. 155).

'Symptomatic COVID-19' cases (of any severity) were classified as either mild, or moderate or severe/critical (per protocol definitions). There were respectively 117 and 351 cases of symptomatic COVID-19 cases, of which 1 and 3 were mild and 116 vs. 348 met the primary endpoint case definition (i.e. were classified as moderate or severe/critical). As the vast majority of symptomatic COVID-19 cases were captured by the primary endpoint definition, the level of efficacy against 'symptomatic COVID-19' of any severity was the same (66.9% [95% CI: 59.07; 73.37]) as efficacy against the primary endpoint.

The level efficacy against COVID-19 of any severity was consistent by using the US FDA Harmonized COVID-19 cases definition (67.2% [95% CI: 59.32; 73.67], based on 114 vs. 345 cases). Again, this shows that vast majority of symptomatic COVID-19 illness cases were captured by the primary endpoint definition.

Cases with an onset at least Day 28:

For the primary endpoint 'moderate to severe/critical COVID-19' with an onset beyond Day 28, there were 66 vs 193 cases in the vaccine vs the placebo group, corresponding to a 66.1% efficacy (Adjusted 95% CI: 55.01; 74.80). The lower limit (LL) of the CI of 55% was well above the pre-specified limit of 30%. Therefore, the primary objective was met for this endpoint.

There were respectively 66 and 195 cases of 'symptomatic COVID-19', of which 0 and 2 were mild and 66 vs. 193 met the primary endpoint case definition (i.e. were classified as moderate or severe/critical). As the vast majority of symptomatic COVID-19 cases were captured by the primary endpoint definition, the level of efficacy against 'symptomatic COVID-19' of any severity was the nearly the same (66.5% [95% CI: 55.50; 75.05]) as efficacy against the primary endpoint. The level efficacy against COVID-19 of any severity was consistent by using the US FDA Harmonized COVID-19 cases definition (66.7% [95% CI: 55.63; 75.23]). The number of cases was 65 vs. 193.

In the 4,156 participants with baseline SARS-CoV-2 seropositivity including non-centrally confirmed cases, 7 COVID-19 cases were reported PCR positive from any source, of which one was confirmed by the central laboratory.

Table 12: Summary of Vaccine Efficacy Against COVID-19 With Onset at Least 14 Days After Vaccination; Per Protocol Set (Study VAC31518COV3001)

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI
Analysis set: Per protocol set		(19630)		(19691)			
Risk set[a]		(19514)		(19544)			
Primary endpoint							
Moderate and severe/critical COVID-19	116	3116.57	348	3096.12	66.9%		(59.03; 73.40)
Age 18-59 years	95	2106.82	260	2094.97	63.7%	(53.87; 71.58)	
Age >=60 years	21	1009.75	88	1001.15	76.3%	(61.58; 86.04)	
Secondary endpoints							
Any symptomatic COVID-19 severity	117	3116.46	351	3095.92	66.9%	(59.07; 73.37)	
Mild	1	3116.46	3	3095.92			
Moderate	102	3116.57	288	3096.12	64.8%	(55.75; 72.21)	
Severe/critical	14	3125.05	60	3122.03	76.7%		(54.56; 89.09)
All symptomatic COVID-19 (BOD)[b]	117	3116.46	351	3095.92	68.1%		(60.26; 74.32)
Age 18-59 years	95	2106.82	260	2094.97	65.8%	(56.22; 73.10)	
Age >=60 years	22	1009.64	91	1000.95	74.5%	(57.91; 84.33)	
Req. Medical intervention[c]	2	3125.92	8	3126.10	75.0%	(-25.28; 97.41)	
Supplementary Endpoints							
Primary endpoint including non-confirmed cases	173	3113.88	509	3089.06	66.3%		(59.86; 71.79)
US FDA Harmonized COVID-19 cases	114	3116.60	345	3096.30	67.2%	(59.32; 73.67)	

Table 13: Summary of Vaccine Efficacy Against COVID-19 With Onset at Least 28 Days After Vaccination; Per Protocol Set (Study VAC31518COV3001)

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI
Analysis set: Per protocol set		(19630)		(19691)			
Risk set[a]		(19306)		(19178)			
Primary endpoint							
Moderate and severe/critical COVID-19	66	3102.00	193	3070.65	66.1%		(55.01; 74.80)
Age 18-59 years	52	2097.60	152	2077.01	66.1%	(53.30; 75.77)	
Age >=60 years	14	1004.39	41	993.64	66.2%	(36.74; 82.99)	
Secondary endpoints							
All SARS-CoV 2 infections	71	3101.59	214	3069.58	67.2%	(56.86; 75.26)	
Any symptomatic COVID-19 severity	66	3102.00	195	3070.53	66.5%	(55.50; 75.05)	
Mild	0	3102.00	2	3070.53			
Moderate	61	3102.00	159	3070.65	62.0%	(48.68; 72.21)	
Severe/critical	5	3106.15	34	3082.58	85.4%		(54.15; 96.90)
Asymptomatic/Undetected SARS-CoV-2 infections[c]	5	3101.59	19	3069.58	74.0%	(27.89; 92.40)	
All symptomatic COVID-19 (BOD)[b]	66	3102.00	195	3070.53	69.0%		(56.68; 77.64)
Age 18-59 years	52	2097.60	152	2077.01	69.3%	(57.42; 77.68)	
Age >=60 years	14	1004.39	43	993.52	67.9%	(38.17; 82.77)	
Req. Medical intervention[d]	0	3106.43	5	3084.42			
Supplementary Endpoints							
Primary endpoint including non-confirmed cases	113	3100.26	324	3065.86	65.5%		(57.15; 72.41)
US FDA Harmonized COVID-19 cases	65	3102.02	193	3070.58	66.7%	(55.63; 75.23)	

The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.
If less than 6 cases are observed for an endpoint then the VE will not be shown.
[a]The risk set are all subjects of the Per Protocol Set excluding subjects that had a positive PCR test between day 1 and day 28.
[b]BOD: Burden Of Disease is a weighted version of the mild, moderate, and severe/critical vaccine efficacies.
[c] A manual review of the reported asymptomatic infections revealed that some of the participants who were listed as asymptomatic had symptoms suggestive of COVID-19.
[d]Medical intervention is defined as hospitalisation, ICU admission, mechanical ventilation, ECMO linked to objective measures as decreased oxygenation, X-ray or CT findings, and as reported by the MRU form.

NE: Not Evaluable

Vaccine Efficacy in Participants who were SARS-CoV-2 seropositive at baseline:

Of 4,156 participants with baseline SARS-CoV-2 seropositivity, 7 COVID-19 cases with onset at least 14 days after vaccination were reported PCR positive from any source, of which one was confirmed by the central laboratory.

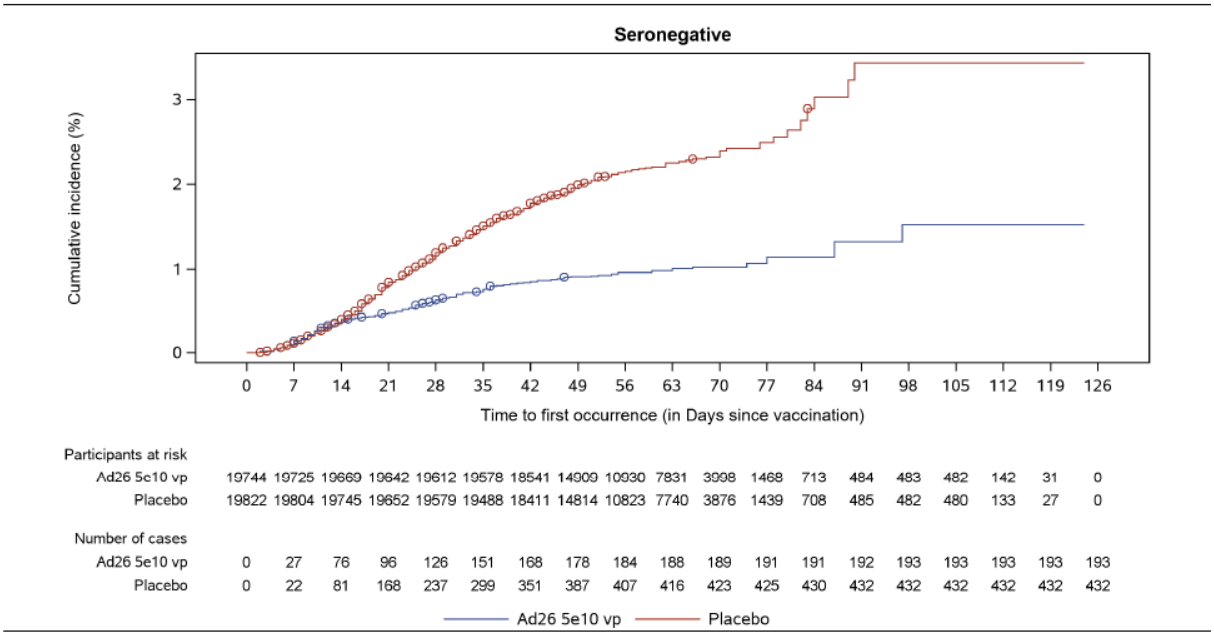
Onset of Protection Against Molecularly Confirmed Moderate to Severe/Critical COVID-19:

The cumulative incidence of molecularly confirmed moderate to severe/critical COVID-19 cases, with onset at least 1 day after vaccination is presented in

Figure 13. The cumulative incidences with onset at least 14 days and 28 days after vaccination were also provided. Vaccine efficacy against molecularly confirmed moderate to severe/critical COVID-19 cases over time is presented in **Figure 14**.

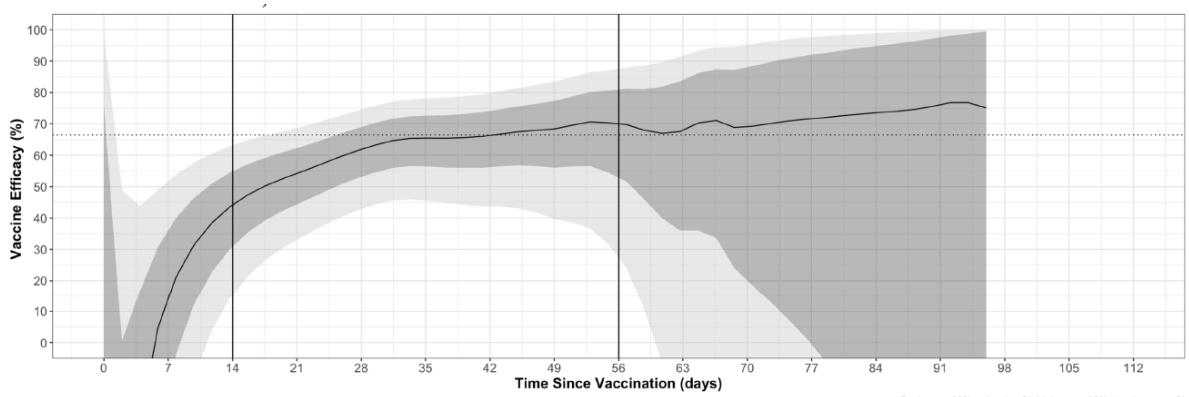
The cumulative incidence of molecularly confirmed moderate to severe/critical COVID-19 cases shows that the curves for the placebo and vaccinated groups start to separate at Day 14, suggesting that the onset of protection is at that time.

The applicant also presented a plot modelling the difference between the curves. This plot suggests that protection is starting to establish around Day 14 up to Day 28-35, presumably related to maturation of functional immune responses and then stabilises up to Day 56. The figure includes CI, which show that the uncertainty around the point estimate are too high (due to small numbers) for adequate interpretation after 56 days.



Baseline seronegativity and seropositivity are based on the serological test at baseline.
Severe/critical cases are marked on the graph.
Adapted from [GEFPE03_B.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\GEFPE03_B.SAS] 23JAN2021, 13:08

Figure 12: Cumulative Incidence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases with Onset at Least 1 Day after Vaccination, Full Analysis Set (Study VAC31518COV3001)



The VE estimates become difficult to interpret with small numbers. Therefore, the VE estimate over time prior to 14 days may be unreliable. Furthermore, since the number of participants with follow-up beyond 56 days significantly decreases, the graphs should be interpreted with caution. This uncertainty is reflected in the width of the confidence intervals around the estimated VE curve beyond that timepoint.

Source: GEFVET01

Figure 13: Vaccine Efficacy Over Time of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases, Full Analysis Set (Seronegative) (Study VAC31518COV3001)

Secondary endpoints

-*Vaccine Efficacy Against Molecularly Confirmed Severe/Critical COVID-19*

More than 23 molecularly confirmed severe/critical (adjudicated) endpoints cases were observed; therefore, the statistical hypothesis testing for VE against molecularly confirmed severe/critical COVID-19 was performed. Results are presented in in the below tables. Cases that could not be adjudicated (such as severe cases that occurred after the cutoff date for adjudication, i.e. 19 January 2021) are included in the primary analysis but not included as severe/critical cases.

Severe cases with an onset at least Day 14:

Of the 116 vs. 348 moderate to severe/critical COVID-19 primary endpoint cases with an onset at least 14 days after vaccination, 14 (12%) vs. 60 (17%) were classified as severe/critical (further referred to as severe). Severe disease was a prespecified inferential endpoint. The point estimate of VE against severe disease was 76.7% (Adjusted 95% CI: 54.56; 89.09). The lower limit of the 95% CI of 55% was well above 30% (the prespecified LL was only 0%).

Severe cases with an onset at least Day 28:

Of the 66 vs. 193 moderate to severe/critical COVID-19 primary endpoint cases with an onset at least 28 days after vaccination, 5 (8%) vs. 34 (18%) were classified as severe/critical (further referred to as severe disease). VE against severe disease was estimated at 85.4% (Adjusted 95% CI: 54.15; 96.90). The lower limit of the CI 95% of 54% was well above 30% (the prespecified LL was only 0%).

Algorithmic Interpretation of the Severe/Critical Case Definition:

Cases were classified as 'severe/critical' based on clinical assessment by the clinical severity adjudication committee. This classification was used in the analyses. Cases were also classified as 'severe/critical' based on a programmed, algorithmic interpretation of the protocol definition (using vital signs, MA-COV, and SAE forms without clinical assessment).

Less cases were classified as severe by the adjudication committee compared to the algorithmic definition (in the FAS, 42 vs. 65 for cases ≤Day 14, 35 vs. 61 for cases Day 15 to Day 28, 39 vs. 55 for >Day 28).

Table 14: Number of Moderate and Severe/Critical COVID-19 Cases Adjudicated; Full Analysis Set (Study VAC31518COV3001) (Source: Table 17 CSR).

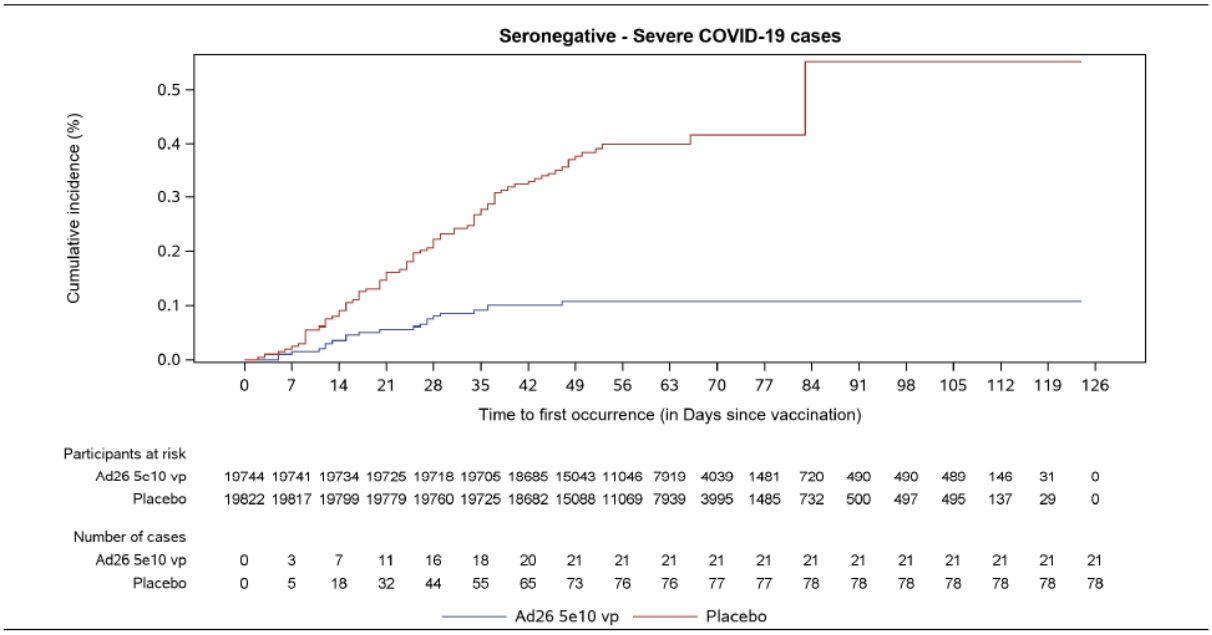
		Molecularly Confirmed cases		Non-centrally Confirmed cases	
	N	# cases adjudicated	#cases programming based	# cases adjudicated	#cases programming based
. Analysis Set: Full analysis set	827				
. <= Day 14					
Moderate		173	150	25	24
Severe/Critical		42	65	6	7
. Day 15-28					
Moderate		161	135	27	25
Severe/Critical		35	61	9	11
. Day >28					
Moderate		205	189	92	82
Severe/Critical		39	55	19	22

Severity for 'cases adjudicated' is based on clinical assessment by the clinical severity adjudication committee outlined per the protocol and SAP. Severity for 'cases programming based' is based on the programmed, algorithmic interpretation of the protocol definition following the algorithm outlined in the SAP.

A sensitivity analysis was performed, using the 'algorithmic interpretation' (for severe case with onset at least 14 days and at least 28 days), and generated overall consistent results compared to the 'adjudication definition'. With the algorithmic definition, efficacy point estimates were also slightly higher for severe compared to moderate disease, but the discrepancy between estimates is lower.

Onset of protection against molecularly confirmed severe/critical COVID-19:

The cumulative incidence curves for severe COVID-19 start to separate at Day 7, suggesting that protection may be established earlier for the severe cases. The plot modelling is still to be interpreted with caution and it is thus difficult to conclude if protection is evolving differently over time for severe compared to moderate cases.



Baseline seronegativity and seropositivity are based on the serological test at baseline.
BOD: Burden Of Disease is based on any molecularly confirmed symptomatic cases.
Adapted from [GEFBO03_B.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\GEFBO03_B.SAS] 23JAN2021, 19:49

Figure 14: Cumulative Incidence of Molecularly Confirmed Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination; Full Analysis Set (Study VAC31518COV3001)

- Vaccine efficacy against asymptomatic or undetected SARS-CoV-2 infection:

The applicant provided an additional interim analysis of the asymptomatic cases based on Day 71 serology results (CSR Addendum) with updated data for participants who had completed their Day 71 visit up to and including 22 January 2021 (serology results cutoff 8 February 2021). Since the supplemental analyses are based on a larger number of N serology results, they supersede the results presented in the interim CSR (see above).

At the time of the primary analysis, 965 participants had their Day 71 samples available, which is only about 2% of the FAS seronegative (n=39,548). This update is based on 2,892 participants with Day 71 serology results, which is 6% of the FAS seronegative and 19% of the number of samples required for the confirmatory analysis of the 'asymptomatic or undetected' endpoint (which will only be performed when 15,000 participants have reached the Day 71 visit).

Per protocol, an 'asymptomatic or undetected SARS-CoV-2 infection' case is ascertained based on seroconversion for N-antibodies or based on positive PCR results, in a participant who did not fulfill the criteria for suspected COVID-19 based on signs and symptoms.

The algorithm in the Statistical Analysis Plan (SAP) identified asymptomatic participants as those who had no symptoms on the day preceding, the day of, or any time after a positive RT-PCR test. A sensitivity analysis was done removing from the case definition the participants who presented symptoms at any time since screening.

Asymptomatic SARS-CoV-2 Infection cases with an onset Day 1 - Day 29:

Respectively 159 and 182 cases were classified as asymptomatic/undetected SARS-CoV-2 infections over the period Day 1 – Day 29, in the vaccine vs. placebo group (FAS seronegative population). This leads to an efficacy point estimate of 12.5% (inconclusive). Respectively 153 and 175 cases who

seroconverted for SARS-COV-2 were detected on that period (serology risk set of participants with a non-S protein result available on Day 29), for an efficacy of 13.1% (inconclusive).

Asymptomatic SARS-CoV-2 Infection cases with an onset beyond Day 28:

There are 22 vs. 54 undetected/asymptomatic cases in the vaccine vs. the placebo group (per protocol risk set), resulting in an efficacy of 59.7% (95% CI: 32.75; 76.64), for the period >29 Days. From the 22 vs. 54 'asymptomatic or undetected SARS-CoV-2 infections' (respectively in the Ad26.COV2.S vs. placebo groups) that occurred beyond Day 29 after vaccination, most (18 vs. 50) were seroconverters (with either no PCR test available, or with a negative PCR [only 4 subjects]). The remaining subjects (4 vs. 4) had a positive PCR result. It is not stated whether these 8 subjects seroconverted as well, and it is not stated whether the result was confirmed at central lab. So, respectively 18 vs. 50 participants seroconverted to COVID-19 (serology risk set of participants with a non-S protein result available on Day 71), for an efficacy of 65.5% (39.91; 81.08).

Sensitivity analysis:

Participants who had no symptoms were identified in the database using an algorithm. However, based on a manual review, it was found that some PCR positive cases classified as asymptomatic/undetected by the algorithm had symptoms 2 days or more prior to the PCR test. The applicant therefore performed a sensitivity analysis restricted to the participants without any COVID-19 symptoms since screening. Results from this analysis are in general line with the former.

Table 15: Summary of Vaccine Efficacy Against Asymptomatic or Undetected SARS-CoV-2 Infections Day 1-Day 29; Full Analysis Set (Study VAC31518COV3001)

	Ad26 5e10 vp		Placebo			
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI
Analysis set: Full analysis set		(21895)		(21888)		
FAS Seronegative at baseline		(19739)		(19809)		
Asymptomatic or undetected SARS-CoV-2 infections (Day 1-29)[b]	159	1561.27	182	1564.07	12.5%	(-8.87; 29.70)
Asymptomatic or undetected SARS-CoV-2 infections without previous symptoms (Day 1-29)[b, d]	87	1556.21	109	1559.33	20.0%	(-6.99; 40.37)
Serology Risk set[a]		(14084)		(14019)		
Seroconverted SARS-CoV-2 (Day 1-29)[c]	153	1114.34	175	1108.22	13.1%	(-8.64; 30.47)
Seroconverted SARS-CoV-2 without previous symptoms (Day 1-29)[c, d]	84	1109.40	108	1103.73	22.6%	(-3.87; 42.52)

[a]Serology set: Participants with an N serology result available on Day 29
[b]A participant will be considered to have experienced asymptomatic or undetected SARS CoV-2 infection if the participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms as detected by the algorithm described in the SAP and has a SARS-CoV-2 positive RT-PCR or molecular test result or develops a positive serology (N-antibodies) test
[c]A participant will be considered serologically converted if the participant develops a positive serology (N-antibodies) test without a SARS-CoV-2 positive RT-PCR before the positive serology test irrespective of whether previous symptoms occurred
[d]A participant is considered without previous symptoms if no COVID-19 symptoms occurred before the positive PCR or serology test at any point in time during the study

Adapted from [TEFSUM02B.RTF]
[VAC31518\VAC31518COV3001\DBR_IA_PRIMARY_SUPP\RE_IA_PRIMARY_SUPP\PROD\TEFSUM02B.SAS] 11FEB2021, 04:58

Table 16: Summary of Vaccine Efficacy Against Asymptomatic or Undetected SARS-CoV-2 Infections From Day 29; Per Protocol Set (Study VAC31518COV3001).

	Ad26 5e10 vp		Placebo			
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI
Analysis set: Per protocol set		(19625)		(19674)		
Risk set		(19301)		(19162)		
Asymptomatic or undetected SARS-CoV-2 infections (day > 29)[b]	22	3099.69	54	3064.15	59.7%	(32.75; 76.64)
Asymptomatic or undetected SARS-CoV-2 infections without previous symptoms (Day > 29)[b,d]	10	3098.02	38	3061.52	74.0%	(46.81; 88.44)
Serology Risk set[a]		(1346)		(1304)		
Seroconverted SARS-CoV-2 (Day > 29)[c]	18	312.23	50	298.82	65.5%	(39.91; 81.08)
Seroconverted SARS-CoV-2 without previous symptoms (Day > 29)[c,d]	10	310.94	37	296.58	74.2%	(47.13; 88.57)

[a]Serology set: Participants with an N serology result available on Day 71
[b]A participant will be considered to have experienced asymptomatic or undetected COVID-19 if the participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms as detected by the algorithm described in the SAP and has a SARS-CoV-2 positive RT-PCR or molecular test result or develops a positive serology (N-antibodies) test
[c]A participant will be considered serologically converted if the participant develops a positive serology (N-antibodies) test without a SARS-CoV-2 positive RT-PCR before the positive serology test irrespective of whether previous symptoms occurred
[d]A participant is considered without previous symptoms if no COVID-19 symptoms occurred before the positive PCR or serology test at any point in time during the study

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Ancillary analyses

Supplementary Analyses Including Centrally and Non-centrally Confirmed Cases

Due to the delay needed to obtain the results from the central lab (average of 14 days), many cases with at least 1 positive PCR result from a local source were not confirmed yet at the time of the primary analysis. There was a longer confirmation time in some countries in the Latin America region and South Africa. Overall, 1,197 cases with at least 1 positive PCR result from any source were reported. Of these, 714 (59.6%) had a positive result from the central lab (positive at UoW), 77 (6.4%) had a positive local result but was not confirmed by the central lab (negative at UoW), for the other cases there is no result yet available at the central lab. The percentage of cases with PCR positive samples but non-confirmed at central lab was quite similar across countries (<10% in all countries), and for the subset of moderate and severe cases. There were no relevant differences across groups (overall and by severity level). When reported to the 791 cases who had at least 1 positive PCR result from any source and a result available from the central lab, 10% of the cases are not confirmed at the central lab.

Table 17: Summary of Confirmed and Non-Confirmed COVID-19 Cases by Onset Period; Full Analysis Set (Study VAC31518COV3001)

	<Day 14	Day 15-28	After Day 28	Entire Period
All Severities				
N	443	273	481	1197
Positive Confirmed UoW	230 (51.9%)	214 (78.4%)	270 (56.1%)	714 (59.6%)
Within study PCR positive - All UoW PCR samples negative	29 (6.5%)	17 (6.2%)	31 (6.4%)	77 (6.4%)
Within study PCR positive - Pending at UoW	147 (33.2%)	0	0	147 (12.3%)
External PCR positive - Within study only negative PCR results	2 (0.5%)	7 (2.6%)	6 (1.2%)	15 (1.3%)
External PCR Positive - Within study no PCR results	4 (0.9%)	7 (2.6%)	18 (3.7%)	29 (2.4%)
Within study PCR results - No samples at UoW yet	31 (7.0%)	28 (10.3%)	156 (32.4%)	215 (18.0%)
Asymptomatic or undetected				
N	122	17	22	161
Positive Confirmed UoW	7 (5.7%)	6 (35.3%)	6 (27.3%)	19 (11.8%)
Within study PCR positive - All UoW PCR samples negative	7 (5.7%)	3 (17.6%)	3 (13.6%)	13 (8.1%)
Within study PCR positive - Pending at UoW	96 (78.7%)	0	0	96 (59.6%)
External PCR positive - Within study only negative PCR results	0	2 (11.8%)	0	2 (1.2%)
External PCR Positive - Within study no PCR results	2 (1.6%)	2 (11.8%)	6 (27.3%)	10 (6.2%)
Within study PCR results - No samples at UoW yet	10 (8.2%)	4 (23.5%)	7 (31.8%)	21 (13.0%)
Mild				
N	14	4	11	29
Positive Confirmed UoW	1 (7.1%)	2 (50.0%)	2 (18.2%)	5 (17.2%)
Within study PCR positive - All UoW PCR samples negative	1 (7.1%)	0	2 (18.2%)	3 (10.3%)
Within study PCR positive - Pending at UoW	9 (64.3%)	0	0	9 (31.0%)
External PCR positive - Within study only negative PCR results	0	0	2 (18.2%)	2 (6.9%)
Within study PCR results - No samples at UoW yet	3 (21.4%)	2 (50.0%)	5 (45.5%)	10 (34.5%)
Moderate				
N	259	208	392	859
Positive Confirmed UoW	180 (69.5%)	171 (82.2%)	223 (56.9%)	574 (66.8%)
Within study PCR positive - All UoW PCR samples negative	18 (6.9%)	12 (5.8%)	19 (4.8%)	49 (5.7%)
Within study PCR positive - Pending at UoW	42 (16.2%)	0	0	42 (4.9%)
External PCR positive - Within study only negative PCR results	2 (0.8%)	2 (1.0%)	3 (0.8%)	7 (0.8%)
External PCR Positive - Within study no PCR results	2 (0.8%)	4 (1.9%)	11 (2.8%)	17 (2.0%)
Within study PCR results - No samples at UoW yet	15 (5.8%)	19 (9.1%)	136 (34.7%)	170 (19.8%)

Table 17: Summary of Confirmed and Non-Confirmed COVID-19 Cases by Onset Period; Full Analysis Set (Study VAC31518COV3001)

Severe/Critical ill				
N	48	44	56	148
Positive Confirmed UoW	42 (87.5%)	35 (79.5%)	39 (69.6%)	116 (78.4%)
Within study PCR positive - All UoW PCR samples negative	3 (6.3%)	2 (4.5%)	7 (12.5%)	12 (8.1%)
External PCR positive - Within study only negative PCR results	0	3 (6.8%)	1 (1.8%)	4 (2.7%)
External PCR Positive - Within study no PCR results	0	1 (2.3%)	1 (1.8%)	2 (1.4%)
Within study PCR results - No samples at UoW yet	3 (6.3%)	3 (6.8%)	8 (14.3%)	14 (9.5%)

UoW = University of Washington (central lab), PCR = Polymerase Chain Reaction.
Analysis updated to only include UoW results which fall after the onset day-7 and exclude DAY 1/SCREENING visits.
For some participants we do not expect swabs to be sent to UoW - either because they only have an external positive swab, or because the swabs they have from within the study are negative.
Data cleaning is still ongoing; hence categorisation can still change.

Table 18: Summary of Vaccine Efficacy Against COVID-19 with Onset at Least 14 Days After Vaccination Including Non-confirmed Cases; Per Protocol Set (Study VAC31518COV3001)

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI
Analysis set: Per protocol set		(19630)		(19691)			
Risk set[a]		(19514)		(19544)			
Primary endpoint							
Moderate and severe/critical COVID-19	173	3113.88	509	3089.06	66.3%		(59.86; 71.79)
Age 18-59 years	137	2104.91	389	2089.20	65.0%	(57.42; 71.44)	
Age >=60 years	36	1008.98	120	999.86	70.3%	(56.53; 80.11)	
Secondary endpoints							
Any symptomatic COVID-19 severity	181	3113.47	516	3088.69	65.2%	(58.70; 70.79)	
Mild	8	3113.47	7	3088.69	-13.4%	(-267.27; 64.07)	
Moderate	154	3113.88	429	3089.06	64.4%	(57.09; 70.57)	
Severe/critical	19	3124.65	80	3120.98	76.3%		(57.87; 87.49)
All symptomatic COVID-19 (BOD)[b]	181	3113.47	516	3088.69	66.4%		(59.92; 71.82)
Age 18-59 years	141	2104.78	391	2089.13	65.5%	(57.76; 71.65)	
Age >=60 years	40	1008.69	125	999.56	69.3%	(55.03; 78.76)	

The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.
If less than 6 cases are observed for an endpoint then the VE will not be shown.
[a]The risk set are all subjects of the Per Protocol Set excluding subjects that had a positive PCR test between day 1 and day 14.
[b]BOD: Burden Of Disease is a weighted version of the mild, moderate, and severe/critical vaccine efficacies.
NE: Not Evaluable

Table 19: Summary of Vaccine Efficacy Against COVID-19 with Onset at Least 28 Days After Vaccination Including Non-Confirmed Cases; Per Protocol Set (Study VAC31518COV3001)

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI
Analysis set: Per protocol set		(19630)		(19691)			
Risk set[a]		(19306)		(19178)			
Primary endpoint							
Moderate and severe/critical COVID-19	113	3100.26	324	3065.86	65.5%		(57.15; 72.41)
Age 18-59 years	87	2096.35	259	2073.04	66.8%	(57.50; 74.25)	
Age >=60 years	26	1003.92	65	992.82	60.4%	(36.78; 75.91)	
Secondary endpoints							
Any symptomatic COVID-19 severity	120	3099.96	328	3065.67	63.8%	(55.27; 70.90)	
Mild	7	3099.96	4	3065.67	-73.1%	(-706.20; 56.00)	
Moderate	105	3100.26	276	3065.86	62.4%	(52.73; 70.24)	
Severe/critical	8	3105.99	48	3082.02	83.5%		(58.23; 94.81)
All symptomatic COVID-19 (BOD)[b]	120	3099.96	328	3065.67	66.0%		(56.33; 73.35)
Age 18-59 years	91	2096.22	260	2073.01	67.2%	(58.00; 74.30)	
Age >=60 years	29	1003.74	68	992.65	61.4%	(38.67; 75.26)	

The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.
If less than 6 cases are observed for an endpoint then the VE will not be shown.
[a]The risk set are all subjects of the Per Protocol Set excluding subjects that had a positive PCR test between day 1 and day 28.
[b]BOD: Burden Of Disease is a weighted version of the mild, moderate, and severe/critical vaccine efficacies.
NE: Not Evaluable

The summaries of VE against COVID-19 with onset at least 14 days and 28 days after vaccination including non-centrally confirmed cases are presented in the tables above. Overall, results are in line with confirmed cases.

- Vaccine Efficacy Against Molecularly Confirmed COVID-19 Requiring Medical Intervention:

Molecularly Confirmed COVID-19 cases Requiring Medical Intervention Collected by the MRU Form:

The MRU form is expected to be completed by the investigator on Day 3-5 and/or Day 29 of the COVID-19 episode. At the time of the primary analysis (cut-off 22 January 2021), not all MRU forms were available, and therefore cases occurring with an onset of approximately 29 days (or less) prior to the cut-off for database lock may not have been included in this analysis per the SAP. Efficacy against molecularly confirmed COVID-19 events requiring medical intervention at least 14 days after vaccination, was estimated at 75.0% (95% CI: -25.28; 97.41). As there were less than 23 COVID-19 cases requiring medical intervention, no inferential testing was performed. This was based on respectively 2 (both severe) vs. 8 (6 severe and 2 moderate) cases in the active vs. the placebo group. At least 28 days after vaccination, 0 case of molecularly confirmed COVID-19 requiring medical intervention were observed in the Ad26.COV2.S group and 5 cases (3 severe and 2 moderate) were observed in the placebo group respectively (as less than 6 cases are observed, the VE and IC were however not shown). Beyond 14 days and 28 days after vaccination, there were thus 2 vs. 8 and 0 vs. 5 cases of molecularly confirmed COVID-19 requiring medical intervention, respectively in the Ad26.COV2.S vs. placebo group. The 2 participants in the Ad26.COV2.S group were hospitalised with no ICU admission. The 8 participants in the placebo group were hospitalised, including 1 admitted at the ICU.

Table 20: Summary of Molecularly Confirmed COVID-19 Cases Requiring Medical Intervention

Treatment Group	Day of Onset*	Case Severity	Medical Encounter Type
Ad26.COV2.S	17	severe/critical	hospital inpatient department
Ad26.COV2.S	15	severe/critical	hospital inpatient department
Placebo	21	severe/critical	hospital inpatient department
Placebo	25	severe/critical	intensive care unit
Placebo	22	moderate	hospital inpatient department
Placebo	37	severe/critical	hospital inpatient department
Placebo	31	severe/critical	hospital inpatient department
Placebo	37	severe/critical	hospital inpatient department
Placebo	45	severe/critical	hospital inpatient department
Placebo	29	moderate	hospital inpatient department

* only cases with onset at least 14 days after vaccination are listed in this table.

Additional post-hoc analysis of all COVID-19 related hospitalisations:

The applicant later presented an additional post-hoc analysis of all COVID-19 related hospitalisations (database cutoff of the primary analysis, 22 January 2021), using a specific algorithm (i.e. implementing a broader search not using only MRU data, but based on all available information from any source, such as SAE forms). In total, 6 vs. 42 COVID-19 related hospitalisations with an onset at least 1 day were observed (2 vs. 29 as of 14 days after vaccination, 0 vs. 16 as of 28 days after vaccination, in the Ad26.COV2.S group). In the per-protocol analysis set, as of 14 days after vaccination, based on 2 versus 29 events, efficacy against COVID-19 related hospitalisations was 93.1% (95% CI: 72.74; 99.20). When restricting the analysis to cases confirmed by the central lab, efficacy was 81.8% (95% CI: 16.69; 98.04), based on 2 vs. 11 events.

Table 21: Summary of Efficacy of First Occurrence of COVID-19 Requiring Medical Intervention with onset at least 1, 14 and 28 Days After Vaccination; (Study VAC31518COV3001)

	Ad26 5e10 vp		Placebo			
	#Cases	Person-Years	#Cases	Person-Years	VE	95% CI
. COVID-19 Related Hospitalizations						
At least 1 day after vaccination, FAS-SN						
Centrally confirmed[a]	6	3202.75	18	3213.07	66.6%	(12.06; 89.13)
Any positive PCR[b]	6	3202.75	42	3211.60	85.7%	(66.13; 95.02)
At least 14 days after vaccination, PP						
Centrally confirmed[a]	2	3125.82	11	3125.93	81.8%	(16.69; 98.04)
Any positive PCR[b]	2	3125.82	29	3125.09	93.1%	(72.74; 99.20)
At least 28 days after vaccination, PP						
Centrally confirmed[a]	0	3106.31	6	3084.38	100.0%	(15.67; 100.00)
Any positive PCR[b]	0	3106.31	16	3083.94	100.0%	(74.26; 100.00)

Onset for this analysis, the earliest of either the onset of the AE linked to COVID-19 or the onset of the COVID-19 episode as determined in the SAP algorithm (based on signs, symptoms from eCOA and MA-COV forms, as well as PCR testing)
[a] Analysis based on a data set of centrally confirmed COVID-19 cases.
[b]Analysis based on a data set including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation

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Co-primary Vaccine Efficacy by Subgroups:

This section describes the results of subgroup analyses for VE for the co-primary endpoints. For subgroups with fewer than 6 cases, no VE was calculated. Vaccine efficacy results across demographic and baseline characteristics are summarised in the below tables:

Vaccine efficacy against molecularly confirmed moderate to severe/critical COVID-19 by age:

- With onset at least 14 Days after vaccination

The efficacy against molecularly confirmed 'moderate to severe/critical COVID-19' at least 14 days after vaccination was established, with slightly higher point estimates in the ≥60 years participants (76.3% [95% CI: 61.58; 86.04]) compared to the 18-59 years participants (63.7% [95% CI: 53.87; 71.58]). Efficacy against cases occurring at least day 14 did not decrease with age. In contrast, there was a slight trend for efficacy to increase with age. The point estimates were 62.1%, 65.2%, 70.4%, 92.0%, in participants 18-39 years, 40-59 years, 60-69 years, and 70-79 years (there were no endpoint cases ≥80 years). It is noted that 60 years may not be a clinically relevant cutoff, and EMA defines the geriatric population as people aged 65 years and older (CPMP/ICH/379/95). In addition, middle and oldest old adults are not well represented in this trial's population (of the ≥60 years participants, 69% are ≥65 years participants but only 11% are ≥75 years). (EMA/CHMP/QWP/292439/2017). Efficacy was 82.4% (95% CI: 63.90; 92.38) in participants ≥65 years.

- With onset at least 28 Days after vaccination:

The efficacy in terms of primary endpoint at least 28 days after vaccination was similar in the 18-59 years participants (66.1% [95% CI: 53.30; 75.77]) and the ≥60 years participants (66.2% [95% CI: 36.74; 82.99]). The point estimates were 66.2%, 66.3%, 62.1%, 79.6%, in participants 18-39 years, 40-59 years, 60-69 years, and 70-79 years (there were no endpoint cases ≥80 years). Efficacy was 74.0% (95% CI: 34.40; 91.35) in participants ≥65 years.

Vaccine efficacy against moderate to severe/critical COVID-19 including non-confirmed cases, by age:

- With onset at least 14 Days after vaccination:

In the extended dataset, the efficacy against 'moderate to severe/critical COVID-19' at least 14 days after vaccination were in line in the 18-59 years participants (65.0% [95% CI: 57.42; 71.44]) and the ≥60 years participants (70.3% [95% CI: 56.53; 80.11]). The point estimates were 63.8%, 66.2%, 64.7%, 85.1%, in participants 18-39 years, 40-59 years, 60-69 years, and 70-79 years (there were no endpoint cases ≥80 years). Efficacy was 76.5% (59.12; 87.30) in participants ≥65 years.

- *With onset at least 28 Days after vaccination:*

The efficacy in terms of primary endpoint at least 28 days after vaccination was similar in the 18-59 years participants 66.8% (95% CI: 57.50; 74.25) and the ≥60 years participants 60.4% (95% CI: 36.78; 75.91). The point estimates were 66.2%, 67.6%, 54.6%, 77.0%, in participants 18-39 years, 40-59 years, 60-69 years, and 70-79 years (there were no endpoint cases ≥80 years). Efficacy was 68.6% (95% CI: 38.60; 85.06) in participants ≥65 years.

Vaccine efficacy against molecularly confirmed moderate to severe/critical COVID-19 by comorbidities:

Efficacy against molecularly confirmed moderate to severe/critical COVID-19 was also demonstrated in participants with and without comorbidities (point estimates 62.9% and 69.1% for cases with onset at least 14 Days after vaccination, and 48.6% and 72.6% for cases with onset at least 28 days after vaccination, for participants with and without comorbidities respectively). Efficacy was estimated for the most common comorbidities (obesity, hypertension, type 2 diabetes mellitus, serious heart conditions), and consistent point estimates were shown. Consistent VE were observed when assessed including non-centrally confirmed cases.

Efficacy cannot be assessed in participants with ≥3 comorbidities due to the limited number of cases, and nothing can be concluded on a potential trend according to the number of comorbidities.

The VE point estimates for those with comorbidities were slightly lower for the participants 'with' vs. 'without' comorbidities. When stratifying by age (18-59 years vs. 60+ and 18-64 years vs. 65 +), there was systematically a lower estimate of VE for those with vs. without comorbidities.

Within the <60 years strata and the <65 years, efficacy was demonstrated for the participants with comorbidities, although the point estimate was slightly lower for the participants with comorbidities.

However, within the ≥60 years strata and the ≥65 years strata, a larger difference in point estimates was observed between participants with and without comorbidities. Efficacy was in addition not significant (lower limit of the 95% CI<0) for the older participants with comorbidities when considering the events with onset >28 days (while it was for the events with onset at least 14 days). For efficacy against cases with onset at least 28 days efficacy was 33.2% (95% CI: -77.59; 76.33) for participants ≥60 years and 44.0% (-85.99; 85.26) for participants ≥65 years.

The 95% CI are however very wide, and estimates are based on few events especially >28 days.

The same pattern was found in the extended data set, although differences were less marked in the extended data set

Summary of Vaccine Efficacy of First Occurrence of Molecularly -Confirmed Moderate to Severe/Critical COVID-19 by Subgroups; Per Protocol Set

Onset at Least 14 Days				Onset at Least 28 Days		
Subgroup	**Ad26.COV2.S Cases (Person-years)**	**Placebo Cases (Person-years)**	**VE% (95% CI)**	**Ad26.COV2.S Cases (Person-years)**	**Placebo Cases (Person-years)**	**VE% (95% CI)**
Sex						
Male	59 (1740.21)	180 (1719.65)	67.6% (56.31; 76.28)	33 (1733.12)	103 (1706.86)	68.4% (52.89; 79.36)
Female	57 (1375.67)	168 (1375.84)	66.1% (53.92; 75.33)	33 (1368.18)	90 (1363.17)	63.5% (45.01; 76.26)
Region						
Latin America	45 (1323.72)	148 (1321.45)	69.6% (57.37; 78.76)	27 (1321.95)	79 (1315.64)	66.0% (46.75; 78.88)
Northern America	32 (1414.94)	135 (1394.15)	76.6% (65.45; 84.63)	19 (1403.79)	67 (1377.40)	72.2% (53.12; 84.22)
Southern Africa	39 (377.91)	65 (380.52)	39.6% (8.77; 60.46)	20 (376.26)	47 (377.61)	57.3% (26.51; 76.03)
Age group (years)						
18-64	107 (2530.27)	297 (2511.23)	64.2% (55.26; 71.61)	60 (2518.73)	170 (2490.11)	65.1% (52.91; 74.45)
≥65	9 (586.31)	51 (584.89)	82.4% (63.90; 92.38)	6 (583.27)	23 (580.54)	74.0% (34.40; 91.35)
≥75	0 (107.37)	8 (99.15)	100% (45.90; 100.00)	0 (106.42)	3 (98.06)	-
Age and comorbidity presence						
18-64, no	67 (1680.95)	198 (1671.90)	66.3% (55.39; 74.88)	38 (1674.32)	127 (1659.82)	70.3% (57.08; 79.92)
≥65, no	2 (295.67)	24 (290.55)	91.8% (67.02; 99.06)	1 (294.08)	14 (289.17)	93.0% (53.84; 99.83)
18-64, yes	40 (849.32)	99 (839.33)	60.1% (41.81; 73.06)	22 (844.41)	43 (830.30)	49.7% (14.02; 71.34)
≥65, yes	7 (290.64)	27 (294.34)	73.7% (38.20; 90.35)	5 (289.19)	9 (291.37)	44.0% (-85.99; 85.26)

Summary of Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19 Including Non-Confirmed Cases by Subgroups; Per Protocol Set

Onset at Least 14 Days				Onset at Least 28 Days		
Subgroup	**Ad26.COV2.S Cases (Person-years)**	**Placebo Cases (Person-years)**	**VE% (95% CI)**	**Ad26.COV2.S Cases (Person-years)**	**Placebo Cases (Person-years)**	**VE% (95% CI)**
Sex						
Male	85 (1739.00)	269 (1715.87)	68.8% (60.07, 75.86)	54 (1732.44)	176 (1704.17)	69.8% (58.85, 78.18)
Female	88 (1374.18)	240 (1372.57)	63.4% (53.06, 71.65)	59 (1367.13)	148 (1361.06)	60.3% (45.99, 71.16)
Region						
Latin America	79 (1322.23)	223 (1318.53)	64.7% (54.14, 73.02)	58 (1320.81)	148 (1313.34)	61.0% (46.87, 71.75)
Northern America	51 (1414.03)	196 (1391.33)	74.4% 65.00, 81.57)	32 (1403.35)	112 (1375.60)	72.0% (58.19, 81.71)
Southern Africa	43 (377.62)	90 (379.20)	52.0% (30.26, 67.44)	23 (376.10)	64 (376.93)	64.0% (41.19, 78.66)
Age group (years)						
18-64	157 (2527.79)	441 (2504.81)	64.7% (57.58, 70.79)	101 (2517.14)	286 (2485.85)	65.1% (56.10, 72.48)
≥65	16 (586.09)	68 (584.25)	76.5% (59.12, 87.30)	12 (583.12)	38 (580.02)	68.6% (38.60, 85.06)
≥75	1 (107.29)	9 (99.08)	89.7% (25.95; 99.77)	0 (106.42)	4 (97.98)	-
Age and comorbidity presence						
18-64, no	100 (1679.43)	285 (1667.87)	65.2% (56.09; 72.54)	67 (1673.20)	199 (1656.95)	66.7% (55.82; 75.11)
≥65, no	3 (295.66)	30 (290.30)	90.2% (68.43; 98.08)	2 (294.07)	20 (288.92)	90.2% (59.56; 98.89)
18-64, yes	57 (848.36)	156 (836.94)	64% (50.88; 73.87)	34 (843.94)	87 (828.89)	61.6% (42.33; 74.97)
≥65, yes	13 (290.43)	38 (293.95)	65.4% (33.55; 83.08)	10 (289.06)	18 (291.10)	44.1% (-27.83; 76.93)

FU duration by age and comorbidities:

Length of follow up was the shortest for participants in the older age group (≥60 years of age), especially for participants with comorbidities. Approximately 50% of the participants 18-59 years without comorbidities were followed for at least 65 days, while for the participants 18-59 years with comorbidities it was 56 days. The length of follow up for participants ≥60 years of age with comorbidities was also shorter than for participants without comorbidities.

-Approximately 50% of the participants ≥60 years without comorbidities were followed for at least 56 days, and 25% were followed for at least 72 days after vaccination.

-Approximately 50% of the participants ≥60 years with comorbidities were followed for at least 50 days, and 25% were followed for at least 56 days after vaccination, and none were followed at least 72 days after vaccination.

Overall, presence of comorbidity and older age were independently associated with shorter follow up duration. This reflects the staggered study design (participants with comorbidities were enrolled later in the trial).

Vaccine efficacy by countries:

A summary of vaccine efficacy against confirmed COVID-19 cases with onset at least 14 days and 28 days after vaccination by country and severity, is presented below. Efficacy against molecularly confirmed moderate to severe/critical COVID-19 was demonstrated in each participating country. Except South Africa, all point estimates were >65% for cases with onset at least 14 days after vaccination (not computed in Chile and Mexico due to small numbers). In South Africa, efficacy was of lower magnitude compared to other region/countries (39.6% [95% CI: 8.77; 60.46] vs. 69.6% [95% CI: 57.37; 78.76] in Latin American countries and 76.6% [95% CI: 65.45; 84.63] in the US, for cases with onset at least 14 days). When evaluated at least 28 days after vaccination, discrepancies between South Africa and the other regions was less marked (57.3% [95% CI: 26.51; 76.03] vs. 66.0% [95% CI: 46.75;78.88] in the Latin America region, and 72.2% [95% CI: 53.12; 84.22] in the US).

Moreover, heterogeneity across regions is much less marked when considering the extended data set (for cases with onset at least 14 days: 52.0% [95% CI: 30.26; 67.44] in South Africa compared to 64.7% [95% CI: 54.14; 73.02] in the Latin America region and 74.4% [95% CI: 65.00; 81.57] in the US). For cases with onset at least 28 days after vaccination, differences across countries are small (64.0% [95% CI: 41.19; 78.66] in South Africa, 61.0% [95% CI: 46.87; 71.75) in the Latin America region and 72.0% [95% CI: 58.19; 81.71] in the US).

Kaplan Meier curves show that onset of protection occurs later in South Africa (around 28 days while overall the onset of protection occurs a 14 days), which may contribute to the lower observed efficacy. It might be hypothesised that Ab and/or T cell responses of higher magnitude are needed for protection against the SA variant.

When taking account both confirmed and non-confirmed cases, the vaccine efficacy against severe disease was high on all three regions (US, Brazil and South Africa).

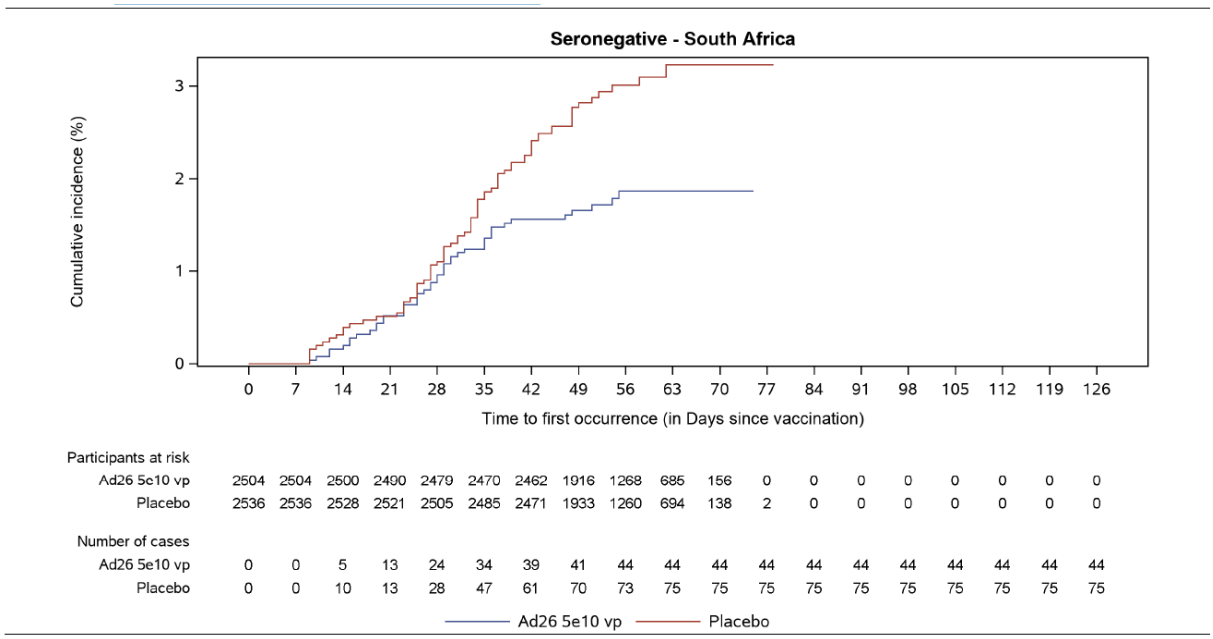


Figure 15: Cumulative Incidence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases with Onset at Least 1 Day After Vaccination By Country (South Africa); Full Analysis Set (Study VAC31518COV3001)

Table 22: Summary of Vaccine Efficacy Against Molecularly Confirmed SARS-Cov2 Infections Cases per Country; Per Protocol Set (Study VAC31518COV3001)

	At least 14 days after vaccination					At least 28 days after vaccination				
	Ad26 5e10 vp		Placebo			Ad26 5e10 vp		Placebo		
	#Cases (N)	PY	#Cases (N)	PY	VE (95% CI)	#Cases (N)	PY	#Cases (N)	PY	VE (95% CI)
Analysis set: PP	(19630)		(19691)			(19630)		(19691)		
Risk set[a]	(19514)		(19544)			(19306)		(19178)		
Argentina										
Moderate and severe/critical COVID-19	3 (1399)	240.26	15 (1409)	241.23	79.9% (29.01; 96.27)	3 (1398)	240.13	8 (1400)	240.60	62.4% (-56.54; 93.58)
Severe/critical	0 (1399)	240.44	1 (1409)	242.50		0 (1398)	240.32	0 (1400)	241.17	
Brazil										
Moderate and severe/critical COVID-19	25 (3370)	556.47	74 (3355)	550.34	66.6% (46.79; 79.66)	11 (3354)	555.41	38 (3312)	547.33	71.5% (43.05; 86.85)
Severe/critical	2 (3370)	558.91	5 (3355)	557.10	60.1% (-143.54; 96.20)	1 (3354)	556.17	4 (3312)	549.88	
Chili										
Moderate and severe/critical COVID-19	1 (531)	83.47	4 (540)	84.05		1 (531)	83.47	2 (538)	83.95	
Severe/critical	0 (531)	83.58	0 (540)	84.54		0 (531)	83.58	0 (538)	84.13	
Columbia										
Moderate and severe/critical COVID-19	15 (1845)	327.90	48 (1858)	326.78	68.9% (43.43; 83.80)	12 (1840)	327.36	28 (1835)	325.05	57.4% (13.59; 80.29)
Severe/critical	1 (1845)	329.04	16 (1858)	330.23	93.7% (59.62; 99.85)	1 (1840)	328.15	8 (1835)	327.04	87.5% (7.08; 99.72)

Table 22: Summary of Vaccine Efficacy Against Molecularly Confirmed SARS-Cov2 Infections Cases per Country; Per Protocol Set (Study VAC31518COV3001)

	At least 14 days after vaccination			At least 28 days after vaccination						
	Ad26 5e10 vp	Placebo		Ad26 5e10 vp	Placebo					
	#Cases (N)	PY	#Cases (N)	PY	VE (95% CI)	#Cases (N)	PY	#Cases (N)	PY	VE (95% CI)
Mexico										
Moderate and severe/critical COVID-19	1 (206)	27.26	0 (220)	29.27		0 (205)	27.22	0 (220)	29.27	
Severe/critical	1 (206)	27.26	0 (220)	29.27		0 (205)	27.22	0 (220)	29.27	
Peru										
Moderate and severe/critical COVID-19	0 (571)	88.36	7 (580)	89.78	100.0% (29.50; 100.00)	0 (571)	88.36	3 (575)	89.44	
Severe/critical	0 (571)	88.36	1 (580)	90.11		0 (571)	88.36	0 (575)	89.55	
USA										
Moderate and severe/critical COVID-19	32 (9119)	1414.94	135 (9086)	1394.15	76.6% (65.45; 84.63)	19 (8958)	1403.79	67 (8835)	1377.40	72.2% (53.12; 84.22)
Severe/critical	4 (9119)	1417.19	14 (9086)	1405.02	71.7% (9.81; 93.21)	1 (8958)	1405.21	4 (8835)	1382.33	
South-Africa										
Moderate and severe/critical COVID-19	39 (2473)	377.91	65 (2496)	380.52	39.6% (8.77; 60.46)	20 (2449)	376.26	47 (2463)	377.61	57.3% (26.51; 76.03)
Severe/critical	6 (2473)	380.27	23 (2496)	383.26	73.7% (33.58; 91.24)	2 (2449)	377.14	18 (2463)	379.20	88.8% (53.34; 98.74)

PY: Person Years; VE: Vaccine Efficacy; CI: Confidence Interval; PP: Per Protocol Set; NE: Not Evaluable.
[a]The risk set are all participants that had a COVID-19 case with onset before day 15 or day 29 respectively.
If less than 6 cases are observed for an endpoint then the VE will not be shown.

Viral genome sequencing of SARS-CoV-2 Spike protein variants

In the time period during which study VAC31518COV3001was conducted, new SARS-CoV-2 lineages emerged in geographical regions where participants for the study were being enrolled. In order to conclude on a potential impact of the infecting SARS-CoV-2 strain on VE, whole genome sequencing of SRAS-CoV-2 in molecularly confirmed COVID-19 cases in the study was performed. Sample prioritisation were country (focusing on South Africa and Brazil), timing of the symptom onset (focusing on cases with an onset of symptoms after Day 14 or Day 28 post-vaccination), and severity of illness (focusing on cases with at least moderate or severe illness). Future selections will be made to ensure that as many cases as possible are sequenced

New SARS-CoV-2 virus lineages are rapidly developing which include mutations in the virus S protein in areas such as the receptor binding domain (RBD) and the N-terminal domain (NTD), that are known targets of neutralising antibodies. Concerns have grown whether vaccines currently in use or in late development that are designed based on the Wuhan-Hu1 variant (as the Ad26.COV2.S) will be able to protect against some of these new virus lineages. Of main concern are the spreading lineages originating from South Africa (lineage B.1.351, variant 20H/501Y.V2, see figure below), the UK (lineage B1.1.7, variant 20I/501Y.V1) and Brazil (lineage P.1, variant 20J/501Y.V3) due to mutations in the RBD and NTD that have shown to impact neutralisation.

At the time of writing this updated report, S gene sequences were completed for 512 of 714 (71.7%) molecularly confirmed cases. Cases were selected for sequencing based on a viral load of >200 copies/mL, sufficient sample volume, sequencing prioritisation of samples from specific countries and severity of illness. The majority of molecularly confirmed infections in both the vaccine and placebo group are moderate/severe diseases.

The interim analysis confirms the predominant circulation of 20H/501Y.V2 in South Africa (86/91 sequences found, 31 vs 55 in the vaccine and placebo groups respectively), the D614G-carrying "WT/ref" strain in the US (190/197 sequences found, 48 vs 142 in the vaccine and placebo groups respectively), and the P.2 (D614G + E484K) lineage in Brazil (86/124 sequences found, 27 vs 59 in the vaccine and placebo groups respectively). The remaining 38/124 sequences found are the Wuhan-Hu1 reference sequence+D614G (10 vs 28 in the vaccine and placebo groups respectively). The 20I/501Y.V1 (UK variant) and the 20J/501Y.V3 (Brazilian P.1 variant) were not found in the analysed samples.

Sequence data was not yet available for all cases and a higher number of samples were sequenced in the placebo group when compared to the vaccine group, which could lead to biases. Therefore, an analysis of vaccine efficacy per SARS-CoV-2 variant is planned upon completion of sequencing.

Vaccine efficacy against severe/Critical COVID-19 by subgroups:

Efficacy against severe disease by age and by comorbidities.

For cases with onset >14 days, efficacy was also demonstrated against molecularly confirmed severe/critical COVID-19 in the 18-59 years, and ≥60 years, as well as in participants with and without comorbidities. Efficacy was 80.5% (95% CI: 57.82; 92.10) in participants 18-59 years of age and 68.5% (95% CI: 18.07; 89.72) in participants ≥60 years of age.

For cases with onset >28 days, for participants ≥60 years of age, and for participants with comorbidities, the lower bound of the 95% CI was <0% (low number of cases).

Point estimates were slightly lower for the older vs. younger adults (with the 60 years cut-off or the 65 years cut of), and for those with vs. without comorbidities.

Differences were smaller in the extended dataset.

In conclusion, efficacy against severe COVID-19 was observed in the participants <60 years, as in those ≥60 years, with no indication of a marked decrease in efficacy over age. Efficacy was also observed in participants with comorbidities. This was a descriptive analysis (non-inferential).

Efficacy against severe disease by country:

For cases with onset at least 14 days, efficacy against molecularly confirmed severe/critical COVID-19 was 73.7% (33.58; 91.24) in South Africa, 71.7% (9.81; 93.21) in the US and 93.7% (59.62; 99.85) in Colombia. Results for cases at least 28 days after vaccination, and results in the extended data set also show efficacy against severe disease in South Africa. In the extended data set, point estimates are similar across the three countries, as shown in the table below.

In conclusion, efficacy against molecularly confirmed severe/critical COVID-19 was observed in South Africa, with a point estimate that was similar compared to the US. CI are however very wide.

Table 23 Summary of vaccine efficacy against COVID-19 and severe COVID-19 for countries with >100 reported cases

		Severity	
	Onset	COVID-19 point estimate (95% CI)	Severe COVID-19 point estimate (95% CI)
US	at least **14 days** after vaccination	74.4% (65.00; 81.57)	78.0% (33.13; 94.58)
	at least **28 days** after vaccination	72.0% (58.19;81.71)	85.9% (-9.38; 99.69)
Brazil	at least **14 days** after vaccination	66.2% (51.01; 77.14)	81.9% (17.01; 98.05)
	at least **28 days** after vaccination	68.1% (48.81; 80.74)	87.6% (7.84; 99.72)
South Africa	at least **14 days** after vaccination	52.0% (30.26; 67.44)	73.1% (40.03; 89.36)
	at least **28 days** after vaccination	64.0% (41.19; 78.66)	81.7% (46.18; 95.42)

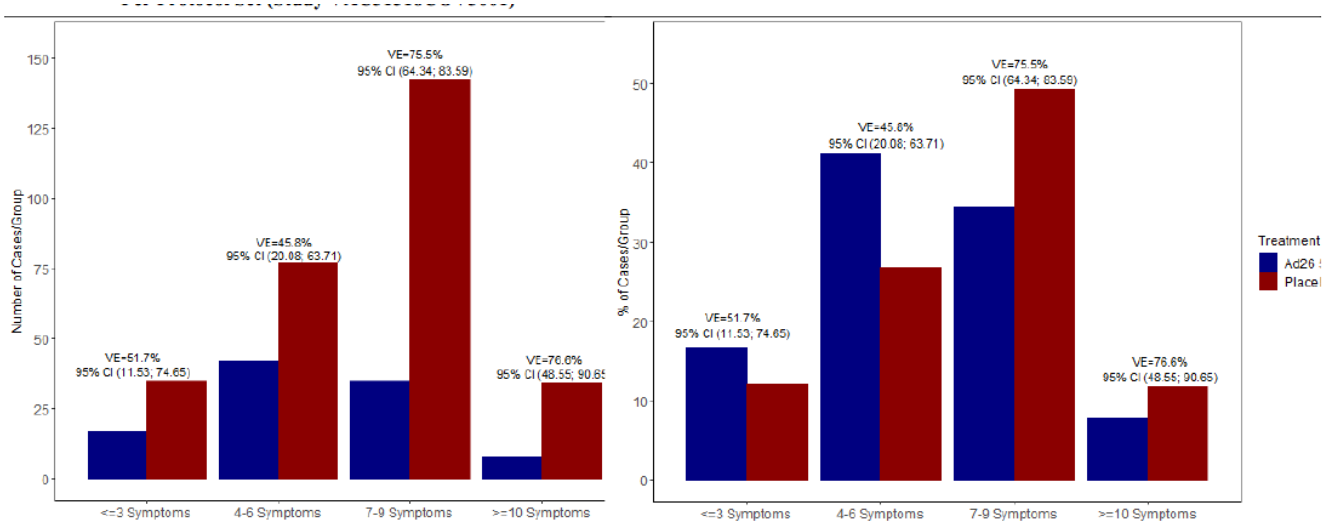
Vaccine impact on symptom severity and number of symptoms:

Symptom severity was graded by the participants in the Symptoms of Infection with Coronavirus-19 (SIC) questionnaire. Participants with a COVID-19 episode are invited to respond daily if he/she had any of a list of prespecified signs or symptoms during the past 24 hours. The SIC consists of 3 separate parts (symptoms rated from 0 to 10 as part 1, fever as part 2, and 4 separate symptoms as part 3) that are scored separately. If a symptom is present, the participant has to rate the severity on a 10-point scale (from none to 10 worst possible). Fever was to be scored (fever score) as the maximum recorded temperature for each day during the COVID-19 episode. The participant also indicated if each of the 4 specific symptoms (i.e. uncontrollable body shaking/shivering, decreased sense of smell, decreased sense of taste, red or bruised looking feet or toes) is either present or absent (from 0 to 3, 0 corresponding to none and 3 to severe). The SIC questionnaire was not always completed (such as when a participant was hospitalised and unable to complete the questionnaire). The total SIC score was calculated for each day of the COVID-19 episode as the mean of all scores. It is however assumed that only the first part was used for the score (with symptoms rated from 0-10). In participants with moderate COVID-19 (>14 days), a slight reduction of symptom severity in the Ad26.COV2.S group compared to the placebo group is observed, over the first week of the episode. No difference is observed as of one week (symptoms are reported up to 6 weeks), and the SIC AUC was similar in the Ad26.COV2.S group compared to the placebo group.

A post-hoc analysis compared the number of symptoms reported by breakthrough cases. As expected, many cases reported many symptoms. Fewer symptoms were reported in breakthrough cases of moderate disease for vaccinated compared to placebo subjects. Consistently, efficacy tended to

increase with an increasing number of symptoms. The interpretation of these data is difficult to reconcile with the fact efficacy could be similar in asymptomatic vs. symptomatic cases.

Figure 16: Summary of Efficacy of first Occurrence of Moderate COVID-19 with Onset at Least 14 Days After Vaccination by Number of Symptoms; Per Protocol Set (Study VAC31518COV3001)

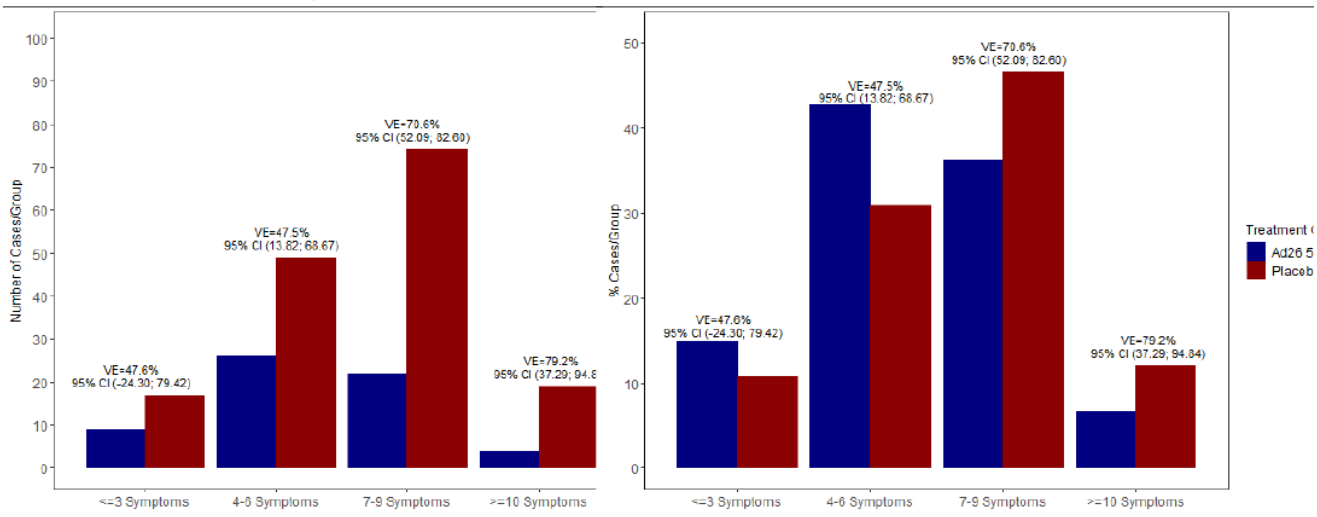


VE: Vaccine Efficacy; CI: Confidence Interval
The Y-axis represents the number of cases and the height of the bar represents the number of cases observed in each category

VE: Vaccine Efficacy; CI: Confidence Interval
The height of the bar represents the percentage of cases per group, calculated as the number of cases in the category divided by the total number of cases in the treatment group times 100.

Adpated from Source: [GEFBO09A.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\GEFBO09A.SAS] 29JAN2021, 11:07

Figure 17: Summary of Efficacy of first Occurrence of Moderate COVID-19 with Onset at Least 28 Days After Vaccination by Number of Symptoms; Per Protocol Set (Study VAC31518COV3001)

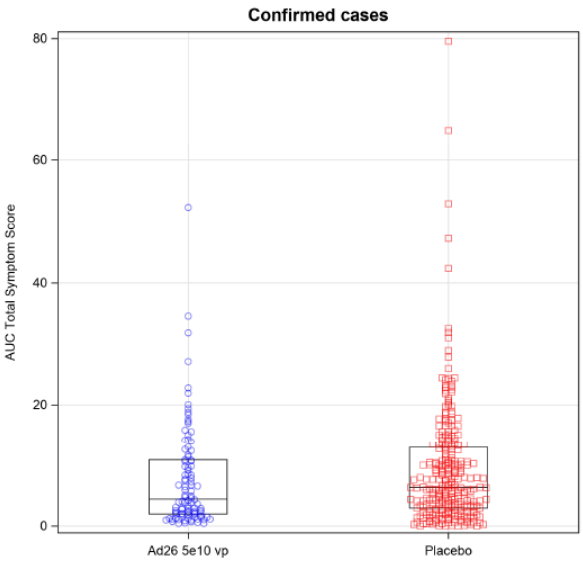


VE: Vaccine Efficacy; CI: Confidence Interval
The Y-axis represents the number of cases and the height of the bar represents the number of cases observed in each category

VE: Vaccine Efficacy; CI: Confidence Interval
The height of the bar represents the percentage of cases per group, calculated as the number of cases in the category divided by the total number of cases in the treatment group times 100.

Adpated from Source: [GEFBO09C.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\GEFBO09C.SAS] 29JAN2021, 11:03

Figure 18: Boxplots of the AUC Symptoms of Infections (SIC) of Molecularly Confirmed Moderate COVID-19 Cases With Onset at Least 14 Days After Vaccination; Per Protocol Set (Study VAC31518COV3001)

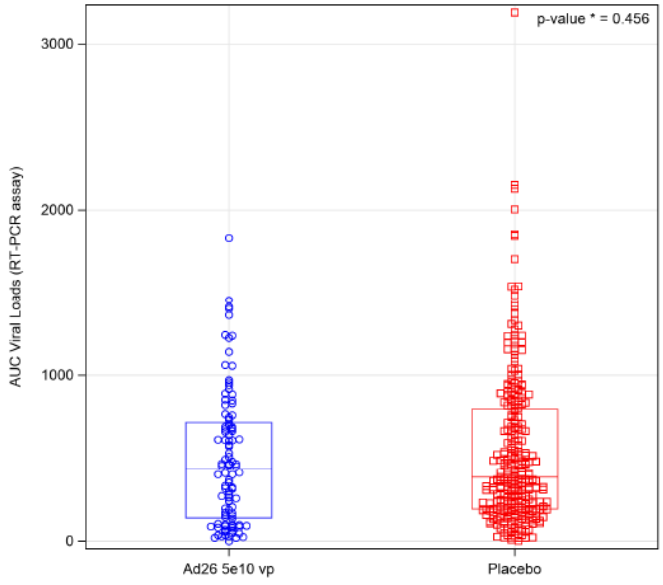


Impact of Ad26.COV2.S vaccination on SARS-CoV-2 viral load:

Nasal swab samples were taken at the start of the COVID-19 episode and every 2 days thereafter until resolution. Saliva swabs were taken every 2 days as of Day 3-5. At this stage, viral load results are preliminary. Not all samples were analyzed at all timepoints for all participants yet. The full viral load profile across the COVID-19 episode was available for 100 participants in the Ad26.COV2.S group and 274 participants in the placebo group with confirmed symptomatic COVID-19 with onset at least 14 days after vaccination (which is the majority of the 116 Ad26COV vs. 348 Placebo cases).

These preliminary data suggest no impact of vaccination on the SARS-CoV-2 viral load levels and duration in COVID-19 breakthrough cases.

Figure 19: Boxplots of the AUC Log10 Viral Load for the Molecularly Confirmed Symptomatic COVID-19 Cases With Onset at Least 14 Days After Vaccination; Per Protocol Set (Study VAC31518COV3001)

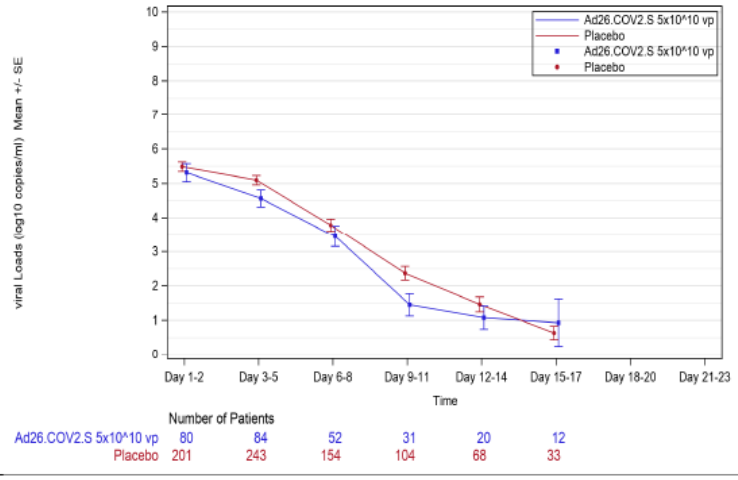


* Wilcoxon Rank Sum test

Values below the LLOQ (indicated as 'Detected' or 'Not Detected') will be imputed with 0 for the AUC calculation. In case some observations are missing at the first timepoint after infection and/ or the last timepoint after challenge, missing values should be imputed with 0.

[GEFVK02_A.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\GEFVK02_A.SAS] 24JAN2021, 09:21

Figure 20: Mean-SE plot of Actual Values of Log10 Viral Load by qRT-PCR over the Molecularly Confirmed Symptomatic COVID-19 Episode with Onset at Least 14 Days After Vaccination; Per Protocol Set (Study VAC31518COV3001)



Individual profiles of viral load over time and log10[viral load] over time since onset of a COVID-19 episode will be summarized by randomized group and severity of COVID-19.

[GEFVK01_A.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\GEFVK01_A.SAS] 24JAN2021, 11:11

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24 Summary of efficacy for trial COV3001

Title: Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older. ENSEMBLE			
Study identifier	VAC31518 (JNJ-78436735), AC31518COV3001, EDMS-RIM-228563, 1.0		
Design	Ongoing multicentre, randomised, double-blind, placebo-controlled Phase 3, pivotal efficacy and safety study that is evaluating efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. Participants were randomised in parallel in a 1:1 ratio to receive 1 dose of Ad26.COV2.S or placebo.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2 years not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Ad26.COV2.S vaccine		1 Ad26.COV2.S dose at $5x10^{10}$ vp 21895 subjects randomised
	Placebo		0.9% NaCl 21888 subjects randomised
Endpoints and definitions	**Co-Primary endpoint**	Moderate and severe/ critical disease	• First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)
	Secondary endpoint	Severe/ critical disease	• First occurrence of molecularly confirmed, severe/critical COVID-19, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)
	Secondary endpoint	Moderate disease	• First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)

	Secondary endpoint	Mild disease	• First occurrence of molecularly confirmed, mild COVID-19, at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed, mild COVID-19, at least 28 days post-vaccination(Day 29)
	Secondary endpoint	All symptomatic (BOD)	• Burden of disease (BOD) endpoint derived from the first occurrence of molecularly confirmed symptomatic COVID-19 (meeting the mild, moderate or severe/critical case definition) with onset at least 14 days post-vaccination (Day 15). • BOD endpoint derived from the first occurrence of molecularly confirmed symptomatic COVID-19 (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 28 days post-vaccination (Day 29)
	Supplementary endpoint	FDA case definition	• First occurrence of molecularly confirmed COVID-19 at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed COVID-19d at least 28 days post-vaccination (Day 29)
Database lock	DATE OF DATA CUTOFF: 22 January 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol set Onset **at least 14 days after vaccination**		
Co-primary endpoint	Treatment group	Ad26.COV.S	Placebo
	Number of subjects	n=19630	n=19691
	Moderate and severe/ critical disease Adj. 95% CI	116 cases Overall VE= 66.9% (59.03, 73.40)	348 cases
	VE% by age group 95% CI	VE Age 18-59 years= 63.7% (53.87, 71.58) VE Age ≥60 years= 76.3% (61.598, 86.04) VE Age ≥65 years= 82.4% (63.90, 92.38) VE Age ≥70 years= 100% (45.90, 100)	

Analysis population and time point description	Per protocol set Onset **at least 28 days after vaccination**		
Co-Primary endpoint	Treatment group	Ad26.COV.S	Placebo
	Number of subjects Moderate and severe/ critical disease Adj. 95% CI	66 cases Overall VE= 66.1% (55.01, 74.80)	193 cases
	VE% by age group 95% CI	VE Age 18-59 years= 66.1% (53.30, 75.77) VE Age ≥60 years= 66.2% (36.74, 82.99) VE Age ≥65 years= 74.0% (34.40, 91.35)	
Analysis description	**Secondary analysis**		

Time point for estimation of efficacy		**14 days after vaccination**	**28 days after vaccination**
Secondary endpoint VE% 95% CI	Severe/ critical disease	76.7% (54.56, 89.09)	85.4% (54.15, 96.90)
	Moderate disease	64.8% (55.75, 72.21)	62.0% (48.68, 72.21)
	Mild disease	Inconclusive	Inconclusive
	All symptomatic (BOD)	68.1% (60.26, 74.32)	69.0% (56.68, 77.64)
Exploratory endpoint	FDA case definition	67.2% (59.32, 73.67)	66.7% (55.63, 75.23)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy results were generated in a randomised, double-blind, placebo-controlled, Phase 3 study in adults ≥18 years of age (COV3001). The study was conducted in the US, several Latin American countries (Argentina, Brazil, Chile, Peru, Mexico, Colombia), and South Africa. Participants were randomised in parallel in a 1:1 ratio to receive Ad26.COV2.S at a dose level of $5x10^{10}$ vp or placebo intramuscularly. Participants were not selected based on anti-SARS-CoV-2 serology. Participants with stable medical conditions were allowed to participate in the study, but those with an abnormal function of the immune system resulting from a clinical conditions or drugs were excluded. The target sample size for the study was approximately 40,000 participants. Randomisation was stratified by site, age

group (≥18-<60 years of age vs ≥60 years of age), and absence/presence of comorbidities that are or might be associated with an increased risk of progression to severe COVID-19.

During the assessment of the cMA, the Ad26.COV2.S vaccine has been granted an Emergency Use Authorization (EUA) in the USA (on February 27, 2021). The applicant, as already planned initially, has submitted two amendments (for study 3001 and for study 1001) to indicate that Ad26.COV2.S vaccine will be offered to enrolled participants who initially received placebo, and that participants and investigators will be unblinded. All participants will be encouraged to remain in the study and continue to be followed for efficacy/effectiveness, safety and immunogenicity as originally planned for up to 2 years post-vaccination. The crossover will result in loss of placebo-controlled follow up. The approach is acceptable considering the circumstances. The inclusion of effectiveness studies (US and EU/UK) in the PhV plan is highly supported.

The primary objective of study COV3001 is to evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19 (with onset at least 14 days post-vaccination and with onset at least 28 days post-vaccination as co-primary endpoints), as compared to placebo, in SARS-CoV-2 seronegative adults. The secondary objectives include the evaluation of efficacy in the prevention of molecularly confirmed: (i) severe/critical COVID-19, (ii) mild COVID-19, (iii) COVID-19 as defined by the US CDC (FDA) harmonised case definition, (iv) all symptomatic COVID-19 (meeting the mild, moderate or severe/critical COVID-19 case definition), in SARS-CoV-2 seronegative adults, (v) COVID-19 requiring medical intervention. In addition, the evaluation of the effect of Ad26.COV2.S on the occurrence of confirmed asymptomatic/undetected infections with SARS-CoV-2 (using SARS-CoV-2 N protein seroconversion) was part of the secondary objectives. The study does not plan for an evaluation effect on SARS-CoV-2 viral RNA load in asymptomatic cases. Viral load will be assessed as part of the secondary objectives in moderate to severe/critical COVID-19. The assessment of efficacy in participants with comorbidities and according to the degree of frailty are relevant exploratory objectives. Frailty has been shown to be an important factor of mortality, independent of age and other comorbidities2. Overall, the study objectives allow for a comprehensive insight into the effect of Ad26.COV2.S on the whole spectrum of COVID-19 illness.

Study procedures allowed for the active surveillance of COVID-19 signs and symptoms, swabbing and virological confirmation of the cases. A broad pre-defined list of symptoms/signs possibly associated with COVID-19 (symptoms from the CDC list and additional symptoms) was used for triggering swabbing to maximise the detection of COVID-19 cases. The study procedures to identify and document the COVID-19 events are deemed appropriate and sufficiently detailed.

Confirmation testing was done by a central lab at Washington University, using the Tier-1 Abbott Realtime SARS-CoV-2 RT-PCR assay, which is multi-target PCR's. Performance data (cross-reactivity and clinical performance) are acceptable. The selected PCR test does not use Spike/RBD targets which minimises the risk of false-negatives as a result of circulating variants with S-dropout. PCR may underperform when mutations appear in the primer/probe target regions, but this risk is mitigated by using dual target detection.

Gene sequencing for the identification of the variants was restricted to the Spike region only. The Swift Biosciences SNAP version 2.0 kit was used on an Illumina sequencing platform. Because the most critical mutations for antibody evasion are located in the Spike protein, the interim analyses on Spike sequences only is sufficient for the time being. The validation document should be provided with the final report (REC).

[2] Hewitt J. et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health 2020; 5: e444–51.

The case definition of moderate COVID-19 includes two sets of criteria using a combination of symptoms and signs. Considering that it is unlikely that mild symptoms occur isolated, it is unclear whether there is an added value (in terms of clinical relevance/specificity) of requiring a combination of symptoms/signs. It is also unclear why the applicant did not use a definition of 'moderate COVID-19' requiring that the first set of criteria is met (irrespective of the presence of mild symptoms/signs), more in line with the NIH definition of moderate COVID-19. Instead, at the moment, cases that would be considered mild disease by other case definitions (i.e. only including symptoms compatible with COVID-19 but without signs of LRT involvement) can meet the protocol definition of moderate disease. In conclusion, the applicant used a complex composite definition of moderate COVID-19, of unclear added value.

The definition for severe/critical COVID-19 is in line with the definition of severe COVID-19 in the FDA guidance on Development and Licensure of Vaccines to Prevent COVID-19 (June 2020). All potential severe/critical COVID-19 cases are adjudicated in a blinded manner by the Clinical Severity Adjudication Committee (CSAC). The applicant indicated that data on the WHO progression scale could not be provided (data were not captured).

The co-primary endpoints consist in a combination of moderate COVID-19 and severe/critical COVID-19, and moderate COVID-19 itself is a composite endpoint. It is not in line with the guidance 'EMA considerations on COVID-19 vaccine approval' which recommends using 'laboratory-confirmed COVID-19 disease of any severity' as the primary endpoint. Limitations were raised in the EMA Rapid scientific advice (EMEA/H/SA/4470/1/FU/1/2020/III). The applicant was advised to consider a simple definition of COVID-19 of any severity, in line with current ECDC, CDC or WHO definitions. This advice was not followed, but in practice, the classification of the cases was very similar when using the primary endpoint case definition or the case definition of 'all symptomatic COVID-19 cases', or the CDC/FDA harmonised case definition.

Therefore, the wording 'COVID-19' is used for the primary endpoint in the SmPC in line with the indication. It would be considered misleading to use the wording 'moderate to severe/critical COVID-19' as it could suggest that the cases corresponding to the primary endpoint tended to be more severe compared to other vaccines, while it is not the case.

The case definition of 'asymptomatic or undetected SARS-COV-2' combining either seroconversion in terms of antibodies against non-S protein (based on systematic sampling in all participants) and/or positive PCR (based on 'accidental' detection of asymptomatic cases) in the absence of criteria for suspected COVID-19 based on the signs and symptoms list is supported. The identification of asymptomatic cases thus mainly relies on SARS-CoV-2 non-S protein seroconversion. A Nucleocapsid protein (NP)-based assay (ELISA N protein assay) was used which is a validated assay, with FDA EUA approval. As routinely testing all asymptomatic participants using swab and PCR testing, despite preferable for a clearer understanding of the impact on asymptomatic infection, is logistically challenging, the applicant's approach is deemed acceptable. However, this will only provide indirect indications about the effect on the risk of infection. More robust estimation of the vaccine's effect on carriage and shedding should be planned. The indirect effect of vaccination on unvaccinated persons, should be studied as well.

From a statistical point of view, this is a fully sequential trial in which the statistical boundaries were based on a truncated sequential probability ratio test (SPRT). Two co-primary endpoints were predefined based on the case definition with onset of at least 14- and 28-days post-vaccination, in the per protocol population set at an overall 2.5% one-sided alpha level. The trial positiveness was predefined for a simultaneously superiority for the two co-primary endpoints against the null value of 30% VE, with both point estimates >50% VE, and ≥5 cases in the placebo arm.

The applicant decided to perform no snapshot analysis but only the primary analysis when the 2-month median follow-up timepoint was reached (database cut-off date: 22 January 2021). Up to the cut-off date, 259 cases meeting the primary endpoints definition of moderate to severe/critical COVID-19 were observed for events with onset at least 28 days after vaccination, exceeding the targeted prespecified number of 154 cases.

The applicant provided the evolution of the different timepoints of the primary analysis on a cumulative basis, from the beginning of the trial, including when the interim analysis was conducted with the minimal data requirements (17/01/2021) and all final available data used in the primary analysis (22/01/2021)

The overrunning is due to the high number of cases cumulated between the data when minimal data requirements for triggering the IA were met (17/01/2021) and the date of data cut-off (22/01/2021). Thus, the overrunning was apparently due to the high number of cases cumulated in just 5 days. Also, there was an unavoidable slight delay needed for the confirmation on the adjudicated cases. In the end, it is understood that some overrunning would have been impossible to avoid given the high incidence rates derived from the epidemiological curves.

Efficacy data and additional analyses

A total of 43,783 randomised participants received the study vaccine (21,895 and 21,888 in the Ad26.COV2.S vs placebo arms). This constitutes the Full Analysis Set (FAS). The primary analysis of VE was based on the Per-protocol Efficacy (PP) population, which includes only participants that were SARS-CoV-2 seronegative at baseline. Of the participants in the FAS, 19,630 (89.7%) and 19,691 (90.0%) were included in PP, respectively in the Ad26.COV2.S vs placebo arms (total of 39,321). Baseline seropositivity for SARS-CoV-2 was the main reason for elimination from the PP set (n=4,217) and/or being PCR positive at baseline the second reason (n=238). Other reasons were major protocol deviations. Reasons for elimination from the PP were balanced across groups. In the FAS, 1,080 (4.9%) and 1,177 (5.4%) participants were unblinded respectively in the vaccine and placebo arms due to request by participants who became eligible to receive an authorised/licensed COVID-19 vaccine. Very few subjects terminated participation prematurely at the time of data cut-off point for the primary analysis (in the FAS 0.2% vs. 0.4%). The main reason for termination was withdrawal by subject.

The study was conducted in the US (44%), various countries of Latin America (41%), and South Africa. The representation of South Africa was substantial (15% in the FAS). The proportion of participants ≥60 years was 35% (in the PP) and the proportion of individuals ≥65 years was 20%. The proportion of subjects ≥75 years was however limited (4% in the PP). Of the participants, 45% were females. There were only few long-term care residents: 0.3% (n=63) vs. 0.4% (n=85) in respective groups (FAS). Participants with comorbidities were well represented. At least one comorbidity was present in 40%-41% (PP-FAS), the most common being obesity (BMI ≥30 kg/m2, 28%-29% in the PP-FAS), hypertension (10%) and type 2 diabetes mellitus (7.5%), followed by serious heart conditions (2.5%), HIV infection (2.5%), asthma (1.5%), COPD (1%). Only very few participants presented comorbidities that are susceptible to significantly affect the immune system (0.2% immunodeficiency condition, <0.1% secondary immunodeficiency, 0.5% malignant neoplasm and 0.5% chronic kidney disease). Only 3% of the subject present 3 or more comorbidities at baseline. The applicant is planning an immunogenicity study in immunocompromised individuals in the PM period.

Baseline characteristics were well balanced across arms, overall and within regions.

Co-Primary endpoint:

Overall, in the PP respectively 54.6% of the Ad26.COV2.S and 54.7% of the placebo participants had a follow-up of at least 2 months after vaccination (calculated as 8 weeks) at the time of the primary analysis. The median follow-up time after vaccination was 58.0 days in both arms.

For the primary endpoint ('moderate to severe/critical COVID-19') with an onset beyond Day 14, efficacy was 66.9% (Adjusted 95% CI: 59.03; 73.40). For the primary endpoint with an onset beyond Day 28, efficacy was 66.1% (Adjusted 95% CI: 55.01; 74.80). Of the 116 vs. 348 cases with an onset beyond Day 14 (respectively in the vaccine vs the placebo group), 66 vs. 193 cases occurred beyond Day 28 (hence nearly half occurred in the period 15-28 days, i.e. 50 vs. 155). The lower limit (LL) of the CI was well above the pre-specified limit of 30%. Therefore, the primary objective was met for both co-primary endpoints.

Symptomatic COVID-19 (any severity):

The number of cases and level of efficacy was consistent by using the US FDA Harmonized COVID-19 case definition (67.2% [95% CI: 59.32; 73.67] based on 114 vs. 345 cases >14 days, 66.7% [95% CI: 55.63; 75.23] based on 65 vs. 193 >28 days).

The endpoint 'symptomatic COVID-19' cases (of any severity) included cases classified as either mild, or moderate to severe/critical (per protocol definitions). At least 14 days after vaccination, there were only 1 and 3 mild cases respectively in the active vs. placebo group, in addition to the 116 vs. 348 cases that met the primary endpoint case definition. The vast majority of 'symptomatic COVID-19' cases were thus captured by the primary endpoint. Therefore, the level of efficacy against 'symptomatic COVID-19' was the nearly identical (66.9% [95% CI: 59.07; 73.37]) >14 days, and 66.5% [95% CI: 55.50; 75.05] >28 days) as the level of efficacy against the primary endpoint. Number of cases and efficacy were thus in line across the primary endpoint and the secondary endpoints 'symptomatic COVID-19' and 'COVID-19 by FDA harmonised definition', as those endpoints actually overlap.

Moderate COVID-19:

Of the primary endpoint 'moderate to severe/critical' COVID-19 cases that occurred at least 14 days after vaccination, most (102 [88%] vs. 288 [83%]) were classified 'moderate COVID-19'. The VE results for 'moderate COVID-19' cases were of 64.8% (95% CI: 55.75, 72.21) and 62.0% (95% CI: 48.68, 72.21) from at least 14 and 28 days, respectively, post-vaccination. The applicant presented post-hoc VE data for participants who only met the first set of symptoms of the 'moderate COVID-19' definition, corresponding to the NIH definition (denoted 'Moderate Part 1'). These cases represented only about a third of the primary endpoint cases (40 [34%] vs. 125 [36%]). The VE (95% CI) for Moderate Part 1 cases with onset at least 14 days and at least 28 days post-vaccination was 68.1% (95% CI: 54.14, 78.24) and 72.6% (95% CI: 55.12, 83.96), respectively.

Severe COVID-19:

Efficacy against severe disease was demonstrated, beyond 14 days and beyond 28 days after vaccination, over a median follow up duration of 58 days. Of the 116 vs. 348 primary endpoint cases with an onset at least 14 days after vaccination, 14 (12%) vs. 60 (17%) were classified as severe/critical (further referred to as severe). The point estimate of VE against severe disease was 76.7% (Adjusted 95% CI: 54.56; 89.09). Of the 66 vs. 193 primary endpoint cases with an onset at least 28 days after vaccination, 5 (8%) vs. 34 (18%) were classified as severe/critical. VE against severe disease was estimated at 85.4% (Adjusted 95% CI: 54.15; 96.90). Severe disease was a prespecified inferential endpoint. The lower limit of the 95% CI of 55% was well above 30% for both endpoints (the prespecified LL was only 0%).

Of the 14 vs. 60 severe cases with onset at least 14 days after vaccination in the Ad26.COV2.S group vs. placebo group, 2 vs. 6 were hospitalised. Three died (all in the placebo group). Based on the data provided during the assessment, it appears that most of the cases were classified as 'severe' based only on abnormal oxygen saturation episodes (SpO2<93%) self-measured (at home). The self-measured SpO2 were not necessarily confirmed by a healthcare worker and values are not corrected for altitude. The CSAS was responsible for taking altitude into account. During the COVID-19 event, at least one measurement was nevertheless taken by the investigator's site or by a home visit by investigator's personnel. All cases were adjudicated as severe based on the clinical independent judgment of the adjudicators, who took into account the overall clinical history of the case. The roles of the Committee and the names of the experts have been provided. Upon request, the Company clarified that all severe cases have an objective finding of low SpO2 or other abnormal sign but that the rationale for the severity assessment was not recorded in the clinical database. Certainly, it would have been desirable to have that information.

Hospitalisation:

Beyond 14 days and 28 days after vaccination, there were 2 vs. 8 and 0 vs. 5 cases of molecularly confirmed COVID-19 requiring medical intervention (as collected via the MRU Form), respectively in the Ad26.COV2.S vs. placebo group. These cases involved hospitalisation only, except one case in the placebo group who required ICU admission and mechanical ventilation. In addition, 2 hospitalised cases in the placebo group were not classified severe. Efficacy against molecularly confirmed COVID-19 events requiring hospitalisation at least 14 days after vaccination, was estimated at 75.0% (95% CI: -25.28; 97.41). This result was non-conclusive, but in line with the point estimate for severe disease. The finding was supported by post-hoc analyses of all COVID-19 related hospitalisations implementing a broader search based on all available information from any source in which there was a favorable case split between the Ad26.COV2.S and placebo groups (beyond 14 days after vaccination 2 vs. 29 in extended data set).

Onset of protection and duration of protection:

The cumulative incidence curves of molecularly confirmed moderate to severe/critical COVID-19 cases (Kaplan Meier) for the placebo and vaccinated groups start to separate at Day 14, suggesting that the onset of protection is at that time. A plot modelling the difference between the curves suggests that protection is starting to be established around Day 14 and increases up to Day 28-35, presumably related to maturation of functional immune responses and then stabilises up to Day 56.

How protection persists beyond 8 weeks remains to be addressed with study COV3001 (specific obligation).

Efficacy by level of severity:

Whether efficacy is higher against severe cases vs. against mild/moderate symptomatic cases is not confirmed yet, but there is a trend it that direction. It is plausible that the immunity induced by vaccination could in some instances be insufficient to prevent mild disease (that is counted in the primary endpoint) but sufficient to prevent the infection evolving into more severe COVID-19 disease. Consistently, efficacy tended to increase with an increasing number of symptoms.

Asymptomatic or undetected cases:

Day 71 samples were available for 2,892 participants, which is only about 6% of the FAS seronegative and 19% of the number of samples required for the confirmatory analysis of the 'asymptomatic or undetected' endpoint (15,000 participants who have reached the Day 71 visit).

Over the period Day 1 – Day 29, the efficacy point estimate was 12.5% (inconclusive) for the prevention of asymptomatic/undetected SARS-CoV-2 infections, and 13.1% (inconclusive) for the

endpoint 'seroconversion only'. In contrast, over the period >28 days, efficacy was 59.7% (95% CI: 32.75; 76.64) for the prevention of undetected/asymptomatic cases, and efficacy in terms of 'seroconversion only' was 65.5% (95% CI: 39.91; 81.08). Most of the 'asymptomatic or undetected SARS-CoV-2 infections' were seroconverters (22 vs. 54 asymptomatic/undetected cases in the vaccine vs. the placebo group, of which 18 vs. 50 were seroconverters). The algorithm in the SAP identified asymptomatic participants as those who had no symptoms on the day preceding, the day of, or any time after a positive RT-PCR test. A sensitivity analysis was performed restricted to the participants without any COVID-19 symptoms since screening and yielded generally similar findings.

Findings related to asymptomatic cases based on N protein serology data are very preliminary. These preliminary data are promising, as they suggest efficacy against asymptomatic SARS-COV-2 infection, at a level that may be consistent with efficacy against symptomatic disease, but this needs to be confirmed over a longer follow with a larger dataset.

Viral load during COVID-19 episodes:

The full viral load profile across the COVID-19 episode was available for a large proportion of the cases. The preliminary data suggest no impact of vaccination on the SARS-CoV-2 viral load levels and duration in COVID-19 breakthrough cases.

Extended data set:

Due to the delay needed to obtain the results from the central lab (average of 14 days), many cases were not confirmed yet at the time of the primary analysis. A repeat of the analysis was performed in which all COVID-19 cases with a positive PCR result were analysed, including all cases with a local lab result, not yet confirmed by the central laboratory. This analysis is referred to as the extended dataset analysis. The total number of cases observed >14 days by this 'extended' definition is 173 in the vaccine group and 509 in the placebo group (i.e. 47 and 131 additional cases). Overall, the primary endpoint analyses and the secondary analyses symptomatic cases are supported by the analysis in the extended data set.

Cases in seropositive subjects:

Of the 4,156 participants SARS-CoV-2 seropositive at baseline, 7 (0.17%) COVID-19 cases were reported as PCR positive from any source (3 vs. 4 in the active vs. placebo group after Day 14) of which one was confirmed by the central laboratory over the study period. In contrast, of the 19,822 placebo subjects in the FAS, 617 PCR positive cases were reported from any source (3.11%) over the approximately two-months study period (average incidence of 19.5 per 100 Person-Years).

Efficacy by age and comorbidities:

The efficacy against molecularly confirmed 'moderate to severe/critical COVID-19' at least 14 days and at least 28 days after vaccination was established in the ≥60 years participants. For events >14 days, efficacy was 76.3% (95% CI: 61.58; 86.04) in participants ≥60 years and 63.7% (95% CI: 53.87; 71.58) in participants 18-59 years. Overall, these results provide clear support for indicating the vaccine in subjects older than 60 years, which is one of the main groups that are at high risk of developing severe COVID-19 complications.

Efficacy against molecularly confirmed moderate to severe/critical COVID-19 was observed both in participants with and without comorbidities (point estimates 62.9% and 69.1% for cases with onset at least 14 days after vaccination, and 48.6% and 72.6% for cases with onset at least 28 days after vaccination, for participants with and without comorbidities respectively). The VE point estimates were lower for the participants 'with' vs. 'without' comorbidities, including when stratifying by age (18-59 years vs. ≥60+ and 18-64 years vs. ≥65 years). When considering efficacy >28 days (where the numbers of events are the lowest) for the older participants with comorbidities, the lower limit of the

95% CI was <0. For those cases with onset at least 28 days efficacy was 33.2% (95% CI: -77.59; 76.33) for participants ≥60 years and 44.0% (-85.99; 85.26) for participants ≥65 years. The 95% CI are very wide, and estimates are based on few events. The same pattern was found in the extended data set, although differences were less marked. It is not considered that there is an efficacy concern in certain subgroups such as older patients with comorbidities. In addition, given the nature of the comorbidities (no immunocompromised participants), there is low biological plausibility for an efficacy issue in these participants. Moreover, efficacy cannot be assessed in participants with ≥3 comorbidities due to the limited number of cases.

Data from subgroups are currently considered preliminary. Length of follow up was the shortest for participants in the older age group (≥60 years of age), especially for those with comorbidities. Differences across subgroups may be strongly influenced by differences in follow up duration. Differences in terms of timing of vaccination could also affect the interpretation of subgroup analyses across age groups and across participants with/without comorbidities (given the emergence of variants for which efficacy could vary). Efficacy by age and comorbidities will need to be assessed over a longer follow-up time to generate more robust estimates. More robust data are expected to be provided in the final report of study COV3001 (SOB). It is noted that follow-up duration may remain an important issue for interpretation of the results in the future given that the elderly participants and those with comorbidities will be unblinded and cross-vaccinated earlier in the trial. Therefore, this should also be addressed in effectiveness studies.

Efficacy by country and circulating variants:

Efficacy against molecularly confirmed moderate to severe/critical COVID-19 was demonstrated in each participating country. Except for South Africa, all point estimates were >65% for events with onset at least 14 days after vaccination (not computed in Chile and Mexico due to small numbers). In South Africa, efficacy was of lower magnitude compared to other region/countries (39.6% [95% CI: 8.77; 60.46] for cases with onset at least 14 days and 57.3% [95% CI: 26.51; 76.03] for cases with onset at least 28 days after vaccination). Heterogeneity across regions is much less marked when considering the extended data set (South Africa: 52.0% [95% CI: 30.26; 67.44] for cases with onset at least 14 days, 64.0% [95% CI: 41.19; 78.66] for cases with onset at least 28 days after vaccination).

There was emergence of new variants reported during the period of the study, especially in South Africa. The applicant performed a sequence analysis restricted to the Spike region. The interim analysis, based on available sequences of approximatively 70% of the cases, confirms the predominant circulation of 20H/501Y.V2 in South Africa (86/91 [94.5%] sequences found, 31 vs 55 in the vaccine and placebo groups respectively) and the D614G-carrying "WT/ref" strain in the US (190/197 [96.4%] sequences found, 48 vs 142 in the vaccine and placebo groups respectively). There was no predominant variant in Brazil, but the P.2 (D614G + E484K) lineage represented two third of the cases in Brazil (86/124 sequences found, 27 vs 59 in the vaccine and placebo groups respectively).

At the time of the current analysis cut-off, analysis of efficacy per variant was not performed. Spike sequence data were available for only 70% of the cases and a higher proportion of samples were sequenced in the placebo group when compared to the vaccine group, which could lead to biases. Therefore, an analysis of vaccine efficacy per SARS-CoV-2 variant is planned upon completion of sequencing

It assumed that the efficacy observed participants living in South Africa is mainly attributable to the SA variant of concern, as this variant was predominant in this country. Efficacy against molecularly confirmed severe/critical COVID-19 was observed in South Africa, with a point estimate that was similar compared to the US. CI are however very wide. Therefore, the efficacy results obtained are

important in that this vaccine would provide relevant protection in case the South African variant spreads to other countries. Data suggest that onset of protection occurs later in South Africa (around 28 days while overall the onset of protection occurs a 14 days).

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study VAC31518COV3001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA, to provide long term follow up data, including data to confirm efficacy in subgroups or data on specific endpoints that were not yet available at the time this assessment was carried out.

2.5.4. Conclusions on the clinical efficacy

Efficacy of Ad26.COV2.S in the prevention of symptomatic COVID-19 was demonstrated in SARS-COV-2 seronegative individuals, over a median follow up period of 8 weeks in a large multiregional trial. Efficacy point estimates were 66.9% and 66.1% for the co-primary endpoints 'moderate to severe/critical COVID-19' with an onset beyond Day 14 and Day 28 respectively. The study showed conclusive evidence since both co-primary efficacy endpoints were met. Efficacy was consistent, with point estimates 65% to 70%, for the various definitions of COVID-19 used in the trial.

The vaccine prevented severe disease. The majority of severe events observed in the trial consisted of COVID-19 with abnormal oxygen saturation episodes (SpO2<93%) often based on participant self-measures. All cases were adjudicated as severe based on the clinical independent clinical judgment of the adjudicators. There was a favourable case split between the vaccine and placebo groups in terms of hospitalised COVID-19. Efficacy point estimates tend to increase with the level of severity of the case definition.

Efficacy was observed in the elderly. Efficacy was also observed in participants with common and stable comorbidities. No data is available for immunocompromised participants.

Efficacy was established in the various regions, including South Africa although at a lower level. New variants were emerging during the study period, and most of the strains circulating in South Africa were the variant of concern 20H/501Y.V2.

Findings related to asymptomatic cases based on N protein serology data are too preliminary to conclude. These preliminary data are nevertheless promising, as they suggest efficacy against asymptomatic SARS-COV-2 infection, at a level that may be consistent with efficacy against symptomatic disease.

Overall, all these efficacy data provide strong evidence for approval of this vaccine for prevention of COVID-19 in subjects of 18 years and older. Of importance, protection in older adults and in subjects infected with a variant (South Africa) SARS-CoV-2 is also demonstrated.

More robust data on efficacy by age and comorbidities are nevertheless expected to be provided in the final report, as well as against the variants.

The duration of protection is not known.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA: the MAH should submit the final clinical study report for the randomised, placebo-controlled, observer-blind study VAC31518COV3001. The study subjects are expected to be followed for 24 months after the first dose.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

2.6. Clinical safety

2.6.1. Patient exposure

Overall, 54,586 adults ≥18 years received Ad26.COV2.S or placebo regardless of the dose level or schedule in studies VAC31518COV3001, VAC31518COV3009, VAC31518COV2001, VAC31518COV1002 and VAC31518COV1001 up cut-off date (22th January 2021) (of which 17,940 participants were ≥60 years of age, 10,746 were ≥65 years, and 1,848 were ≥75 years). Of these 54,586 adults, 1,596 adults received 2 doses of Ad26.COV2.S or placebo.

An overview of the safety database for participants that received $5x10^{10}$ vp Ad26.COV2.S up to the cut-off date of each analysis for each study is provided in **Table 25**.

Table 25: Number of Participants that Received $5x10^{10}$ vp Ad26.COV2.S Included in the Safety Analysis

	Number of Participants Included in Analysis of Solicited, Unsolicited[a], and Immediate AEs[b]		Number of Participants Included in Analysis of Deaths and SAEs		
	Younger adults[c]	Older adults[d]	Younger adults[c]	Older adults[d]	Total
VAC31518COV1001	162	161	363	161	524
VAC31518COV1002	51	NA	51	50	101
VAC31518COV2001	178	98	178	98	276
VAC31518COV3001	2,036[e]	1,320[e]	14,564	7,331	21,895
VAC31518COV3009	NA	NA	3,184	1,265	4,449
Total	**2,427**	**1,579**	**18,340**	**8,905**	**27,245**[f]

NA: Not available. Safety analysis currently not available for this age group.

a Solicited AEs collected from the day of vaccination until 7 days after each vaccination. Unsolicited AEs collected from the day of vaccination until 28 days after each vaccination.

b Immediate AEs collected within 30 minutes after vaccination (COV3001 only).

c Younger Adults: ≥18 to ≤55 years for COV1001 and COV2001; ≥20 to ≤55 years for COV1002; ≥18 to <60 years for COV3001 and COV3009.

d Older Adults: ≥65 years for COV1001 and COV2001; ≥60 years for COV3001 and COV3009.

e In study COV3001, solicited and unsolicited AEs are only collected for the safety subset.

f Includes exposure to a single-dose or 2-dose vaccination regimen with Ad26.COV2.S at the selected dose level ($5x10^{10}$ vp) with at least a 28-day interval between doses for the 2-dose regimen.

Main clinical study: VAC31518COV3001

In COV3001, a total of 44,325 participants were randomised of whom 43,783 were vaccinated (21,895 in the Ad26.COV2.S $5x10^{10}$ vp group and 21,888 in the placebo group) and included in the Full analysis set (FAS). Of these 43,783 participants, 6,736 (3,356 in the Ad26.COV2.S $5x10^{10}$ vp group and 3,380 in the placebo group) were included in the safety subset. Of the participants in the FAS, none had completed the study at the time of the analysis.

Of the participants in the FAS, 49 subjects (0.2%) in the Ad26.COV2.S $5x10^{10}$ vp group and 96 subjects (0.4%) in the placebo group, had discontinued the study prematurely, mainly due to

withdrawal of consent (35 [0.2%] participants and 66 [0.3%] participants in the Ad26.COV2.S and placebo group, respectively).

At the time of the primary analysis, the median follow-up after vaccination was 58 days in both groups. Longer safety follow-up of >2 months is available for 23,903 participants in the FAS: 11,948 participants in the Ad26.COV2.S group (54.6%) and 11,955 in the placebo group (54.6%). However, only 34 participants in the Ad26.COV2.S group (0.2%) and 31 in the placebo group (0.1%) have been followed for close to 4 months. Long-term safety is identified as a missing information in the RMP.

Demographic and baseline: Main clinical study: VAC31518COV3001

In the FAS, with a median age of 52 years of age, there were 21,895 adults ≥18 years of age, including 17,636 adults 18-64 years of age (80.5%) and 4,259 adults ≥65 years of age (19.5%) (with 809 adults ≥75 years of age - 3.7%), including 8,936 adults with comorbidities (40.8%) (with 2,271 adults ≥65 years of age with comorbidities – 10.4%), and including 2,151 adults seropositive at baseline (9.8%), who received Ad26.COV2.S at the selected dose level of 5x1010 vp.

In the safety subset, with a median age of 54, there were 3,356 adults ≥18 years of age, including 2,593 adults 18-64 years of age (77.3%) and 763 adults ≥65 years of age (22.7%) (with 150 adults ≥75 years of age – 4.5%), and including 1,135 adults with comorbidities (33.8%) (with 341 adults ≥65 years of age with comorbidities – 10.2%), and including 154 adults seropositive at baseline (4.6%), who received Ad26.COV2.S at the selected dose level of 5x1010 vp.

There were 1,320 subjects ≥60 years of age in Ad26.COV2.S group and 1,331 subjects ≥60 years of age in placebo group. This is in line with protocol requirements which requested to have at least 2,000 elderly participants ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 among the approximately 6,000 participants in the safety subset (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients).

In the FAS and the safety subset, the demographic and baseline characteristics were similar among participants who received Ad26.COV2.S or placebo

The demographic profile of Ad26.COV2.S was generally similar between the safety subset and the FAS, with the exception of race, country, and serostatus at baseline. In the FAS, participants were mainly from US (44.1%), Brazil (16.6%), South Africa (15%); in addition to Colombia (9.7%), Argentina (6.8%), Peru (4%), Chile (2.6%) and Mexico (1.1%). In the safety subset were included only participants from the US (51.5%), Brazil (38.5%) and South Africa (10.1%), for practical reason (Cf. methodology section). In the safety subset, the proportion of White participants was greater (83.4%) compared to the FAS (58.7%). The proportion of participants who were SARS-CoV-2 seropositive at baseline was lower (4.6%) compared to the FAS (9.6%).

Demographic and baseline: Other clinical studies

In the Phase 1 and 2 studies (VAC31518COV1001 [Cohorts 1a and 3], VAC31518COV1002, and VAC31518COV2001), demographics and baseline characteristics were generally well balanced between the Ad26.COV2.S vaccine groups and the placebo groups. In Studies VAC31518COV1001 and VAC31518COV2001, most participants were white. Study VAC31518COV1002 was conducted in Japan only. In study VAC31518COV2001, the proportion of males was 63.4 % versus 36.6% of females.

In study VAC31518COV1001 Cohort 1b (participants aged ≥18 to ≤55 years), a total of 25 participants were randomised and vaccinated. By the cut-off date of 11/01/2021, all participants had completed the study treatment or had discontinued early. Overall, 56.0% of participants were female and 44.0% were male. The median age was 42 years (range: 22 to 52 years) and the median BMI was 24.8 kg/m^2 (range: 18.8 to 29.9 kg/m^2). Most participants were White (88.0%).

2.6.2. Adverse events

Solicited Adverse Events

Study VAC31518COV3001

In study VAC31518COV3001 solicited adverse events were collected in the safety subset group

During the 7-day post-vaccination period, the frequency of solicited AEs was higher in participants in the Ad26.COV2.S group (66%), compared to participants in the placebo group (41.9%) (mainly grade 1 and 2) in the safety subset group.

Table 26: Overall Summary of Solicited Adverse Events; Safety Subset (Study VAC31518COV3001)

	Ad26 5e10	Placebo
Analysis set: Safety Subset	3356	3380
Post-dose	3356	3380
Subjects with 1 or more:		
Solicited AE	2216 (66.0%)	1417 (41.9%)
Solicited AE of worst grade 3	75 (2.2%)	25 (0.7%)
Solicited AE of worst grade 4	0	0
Solicited local AE	1687 (50.3%)	658 (19.5%)
Solicited local AE of worst grade 3	23 (0.7%)	6 (0.2%)
Solicited local AE of worst grade 4	0	0
Solicited systemic AE	1853 (55.2%)	1188 (35.1%)
Solicited systemic AE of worst grade 3	61 (1.8%)	21 (0.6%)
Solicited systemic AE of worst grade 4	0	0
Solicited systemic AEs considered to be related to study vaccine	1819 (54.2%)	1131 (33.5%)
Solicited systemic AEs of grade 3 or higher considered to be related to study vaccine	60 (1.8%)	20 (0.6%)

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. Relationship to vaccine is assessed by the investigator.

Solicited local reactions

During the 7-day post-vaccination period, the frequency of solicited local AEs was higher in participants in the Ad26.COV2.S group (50.3%), compared to participants in the placebo group (19.5%) (table below). The most frequently reported solicited local AE was vaccination site pain with a frequency that was higher in participants in the Ad26.COV2.S group (48.7%), compared to participants in the placebo group (16.7%). Vaccination site erythema (7.3% vs. 3.9%, respectively) and vaccination site swelling (5.3% vs. 1.6%) were also more frequent in participants in the Ad26.COV2.S group.

Local solicited adverse events were mainly grade 1 or 2. The frequency of Grade 3 solicited local AEs was low overall, but higher in participants in the Ad26.COV2.S group compared to participants in the placebo group: vaccination site pain (0.3% vs. 0.1%, respectively), vaccination site erythema (0.2% vs. 0.1%), and vaccination site swelling (0.2% vs. 0.1%) (no grade 4). All solicited local AEs are considered related to study vaccination by definition. These local solicited AEs are adequately specified, with the appropriate frequencies, in the ADR table in the SmPC.

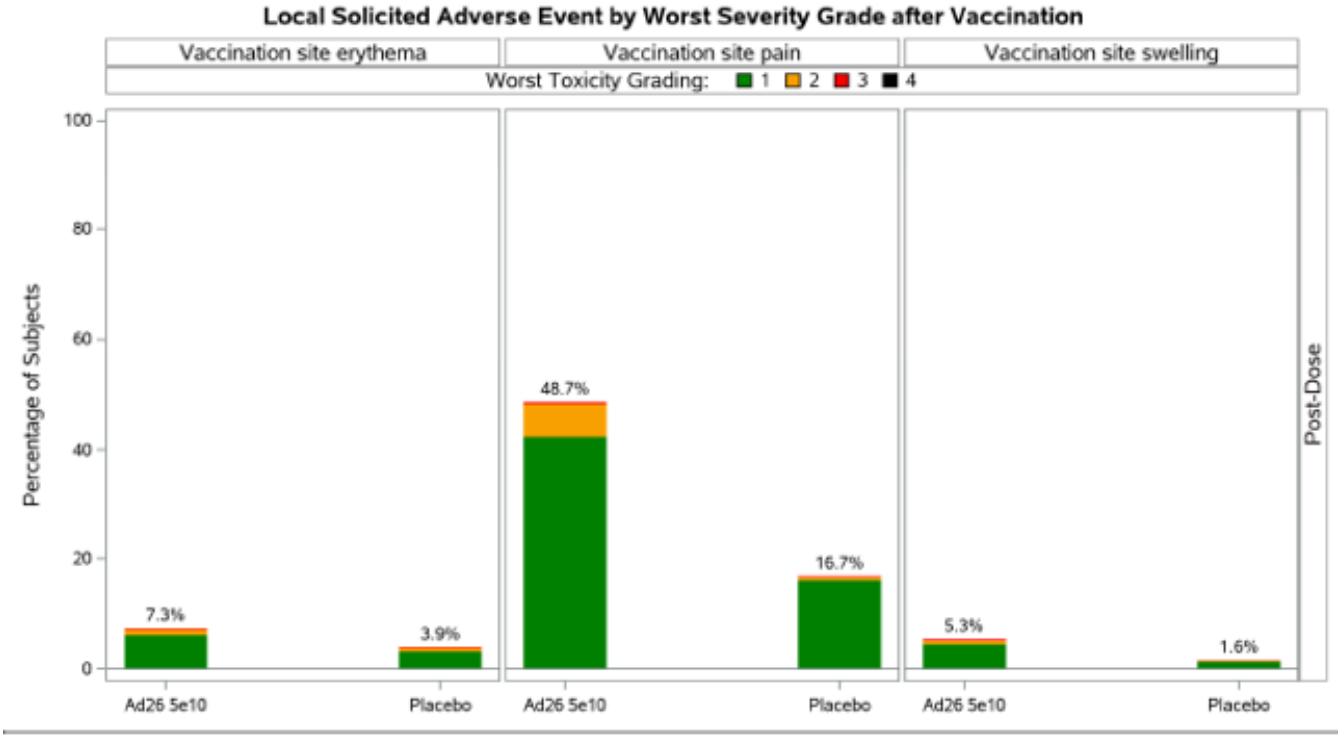
Table 27: Number of Subjects with Local Solicited Adverse Events by Derived Term and Worst Severity Grade; Safety Subset (Study VAC31518COV3001)

	Ad26 5e10	Placebo
Analysis set: Safety Subset	3356	3380
Post-dose	3356	3380
Subjects with 1 or more Local AEs		
Any	1687 (50.3%)	658 (19.5%)
Grade 1	1441 (42.9%)	609 (18.0%)
Grade 2	223 (6.6%)	43 (1.3%)
Grade 3	23 (0.7%)	6 (0.2%)
Vaccination Site Erythema		
Any	245 (7.3%)	131 (3.9%)
Grade 1	207 (6.2%)	108 (3.2%)
Grade 2	31 (0.9%)	21 (0.6%)
Grade 3	7 (0.2%)	2 (0.1%)
Vaccination Site Pain		
Any	1634 (48.7%)	565 (16.7%)
Grade 1	1425 (42.5%)	542 (16.0%)
Grade 2	198 (5.9%)	21 (0.6%)
Grade 3	11 (0.3%)	2 (0.1%)
Vaccination Site Swelling		
Any	178 (5.3%)	53 (1.6%)
Grade 1	150 (4.5%)	45 (1.3%)
Grade 2	21 (0.6%)	6 (0.2%)
Grade 3	7 (0.2%)	2 (0.1%)

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The event experienced by the subject with the worst severity grade is used. If a subject has missing severity grade for a specific adverse event, the subject is counted in the 'Any' row for that adverse event.

The frequencies of solicited local AEs are graphically presented in **Figure 22** below.

Figure 21: Presentation of Local Solicited Adverse Events by Worst Severity Grade After any Vaccination; Safety Subset (Study VAC31518COV3001)



All solicited local AEs were transient in nature and reported as resolved. The median time to onset of the selected solicited local AEs was within 2 days after vaccination with Ad26.COV2.S (including day of vaccination), and within 1 to 2 days with placebo.

The median duration for the most frequent solicited local AEs (vaccination site pain, vaccination site erythema) was 2 days after vaccination with Ad26.COV2.S or placebo. The median duration for vaccination site swelling was 3 days after vaccination with Ad26.COV2.S and 1 days after placebo.

Solicited systemic reactions

During the 7-day post-vaccination period, the frequency of solicited systemic AEs was higher in participants in the Ad26.COV2.S group (55.2%), compared to participants in the placebo group (35.1%) (table below). The most frequently solicited systemic AEs were headache (39% in Ad26.COV2.S group vs. 23.8% in the placebo group), fatigue (38.3% vs. 21.6%, respectively), and myalgia (33.2% vs. 12.8%). Nausea were reported at 14.2% in Ad26.COV2.S group vs. 9.7% in the placebo group. Pyrexia (defined as body temperature ≥38.0°C, as recorded by the participants) was reported in 302 (9.0%) participants in the Ad26.COV2.S group, compared to 20 (0.6%) of participants in the placebo group. These systemic solicited AEs are adequately specified, with the appropriate frequencies, in the ADR table in the SmPC.

Most solicited systemic AEs were Grade 1 or Grade 2 in severity (no grade 4). The frequency of Grade 3 solicited systemic AEs was low overall, but higher in participants in the Ad26.COV2.S group compared to participants in the placebo group. The most frequently reported Grade 3 solicited systemic AEs reported for fatigue (35 participants – 1%) and myalgia (32 participants – 1%) during the 7-day postvaccination period. Grade 3 headache were reported by 23 subjects (0.7%), and grade 3 nausea by 6 subjects (0.2%). Grade 3 pyrexia was reported in 8 (0.2%) participants in the Ad26.COV2.S group. Among these 8 participants, 7 participants were in the ≥18 to <60 years age

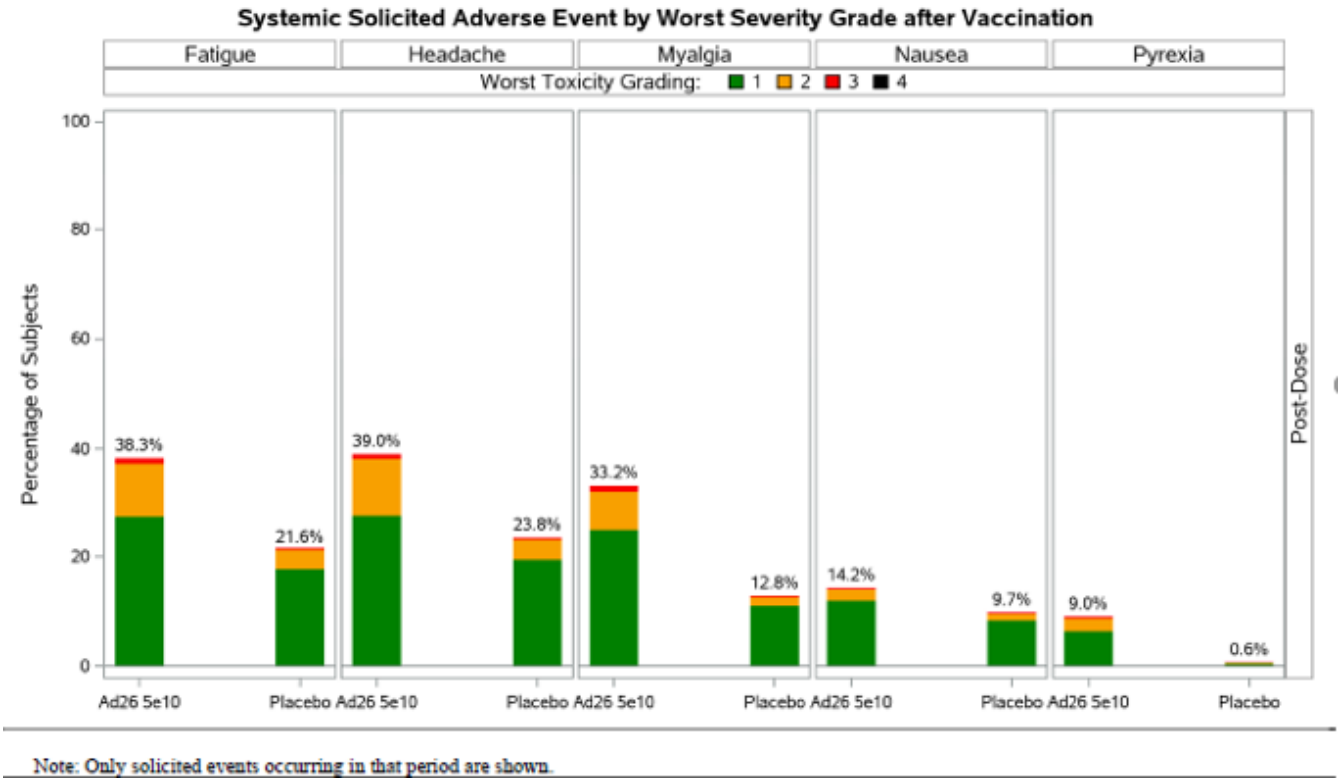
group and these 7 participants were all <35 years of age. In the ≥60 years age group, 1 participant reported Grade 3 pyrexia. No Grade 3 pyrexia was reported in the placebo group.

Table 28. Number of Subjects With Systemic Solicited Adverse Events by Derived Term and Worst Severity Grade; Safety Subset (Study VAC31518COV3001)

	Ad26 5e10	Placebo
Analysis set: Safety Subset	3356	3380
Post-dose	3356	3380
Subjects with 1 or more Systemic AEs		
Any	1853 (55.2%)	1188 (35.1%)
Grade 1	1217 (36.3%)	938 (27.8%)
Grade 2	575 (17.1%)	229 (6.8%)
Grade 3	61 (1.8%)	21 (0.6%)
Fatigue		
Any	1286 (38.3%)	729 (21.6%)
Grade 1	929 (27.7%)	601 (17.8%)
Grade 2	322 (9.6%)	119 (3.5%)
Grade 3	35 (1.0%)	9 (0.3%)
Headache		
Any	1308 (39.0%)	805 (23.8%)
Grade 1	935 (27.9%)	658 (19.5%)
Grade 2	350 (10.4%)	138 (4.1%)
Grade 3	23 (0.7%)	9 (0.3%)
Myalgia		
Any	1115 (33.2%)	432 (12.8%)
Grade 1	848 (25.3%)	375 (11.1%)
Grade 2	235 (7.0%)	51 (1.5%)
Grade 3	32 (1.0%)	6 (0.2%)
Nausea		
Any	478 (14.2%)	329 (9.7%)
Grade 1	402 (12.0%)	284 (8.4%)
Grade 2	70 (2.1%)	39 (1.2%)
Grade 3	6 (0.2%)	6 (0.2%)
Pyrexia		
Any	302 (9.0%)	20 (0.6%)
Grade 1	214 (6.4%)	16 (0.5%)
Grade 2	80 (2.4%)	4 (0.1%)
Grade 3	8 (0.2%)	0

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The event experienced by the subject with the worst severity grade is used. If a subject has missing severity grade for a specific adverse event, the subject is counted in the 'Any' row for that adverse event.

Figure 22: Graphical Presentation of Systemic Solicited Adverse Events by Worst Severity Grade After any Vaccination; Safety Subset (Study VAC31518COV3001)



Most solicited systemic AEs after vaccination were considered to be related to study vaccine (98.16% (1819/1853) of the solicited systemic AEs were considered related to the study vaccine, and 95.2% (1131/1188) to the placebo). In the Ad26.COV2.S group, the most frequently reported solicited systemic AEs related to vaccination were headache (38.2%), fatigue (37.4%), and myalgia (32.6%). Related nausea was reported by 13.9%, and related pyrexia by 8.9%.

Table 29: Number of Subjects With Systemic Solicited Adverse Events Related to Vaccination by Derived Term; Safety Subset (Study VAC31518COV3001)

	Ad26 5e10	Placebo
Analysis set: Safety Subset	3356	3380
Post-dose	3356	3380
Subjects with 1 or more Systemic AEs related to vaccination	1819 (54.2%)	1131 (33.5%)
Fatigue	1254 (37.4%)	705 (20.9%)
Headache	1282 (38.2%)	750 (22.2%)
Myalgia	1093 (32.6%)	417 (12.3%)
Nausea	465 (13.9%)	310 (9.2%)
Pyrexia	298 (8.9%)	16 (0.5%)

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. Relationship to vaccine is assessed by the investigator.

Regarding the severity, most Grade 3 solicited systemic AEs were considered as related to Ade26.COV2.s, there was only one report of grade 3 headache that was not considered related to the study vaccine. In the Ad26.COV2.S group, the most frequently reported grade 3 solicited systemic AEs related to vaccination were fatigue (1%), myalgia (1%) and headache (0.7%). Grade 3 related nausea and pyrexia were reported by 0.2% each.

Table 30: Number of Subjects With Systemic Solicited Adverse Events related to vaccination by Derived Term and Worst Severity Grade of at Least Grade 3; Safety Subset (Study VAC31518COV3001)

	Ad26 5e10	Placebo
Analysis set: Safety Subset	3356	3380
Post-dose	3356	3380
Subjects with 1 or more Systemic AE grade 3 or higher		
Any	60 (1.8%)	20 (0.6%)
Grade 3	60 (1.8%)	20 (0.6%)
Fatigue		
Any	35 (1.0%)	9 (0.3%)
Grade 3	35 (1.0%)	9 (0.3%)
Headache		
Any	22 (0.7%)	9 (0.3%)
Grade 3	22 (0.7%)	9 (0.3%)
Myalgia		
Any	32 (1.0%)	5 (0.1%)
Grade 3	32 (1.0%)	5 (0.1%)
Nausea		
Any	6 (0.2%)	6 (0.2%)
Grade 3	6 (0.2%)	6 (0.2%)
Pyrexia		
Any	8 (0.2%)	0
Grade 3	8 (0.2%)	0

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The event experienced by the subject with the worst severity grade is used. If a subject has missing severity grade for a specific adverse event, the subject is counted in the 'Any' row for that adverse event.

Most solicited systemic AEs were transient in nature and reported as resolved. Overall, the median duration of the selected solicited systemic AEs was similar in both groups (1 to 2 days after vaccination with Ad26.COV2.S or with placebo), and also the median time to onset (within 2 days after vaccination with Ad26.COV2.S and within 2 to 3 days after vaccination with placebo)

Supportive studies (COV1001, COV1002 and COV2001)

Overall, the solicited and unsolicited AEs in supportive studies were consistent with the pivotal phase 3 COV3001 study.

Solicited AEs after dose 1

In all supportive studies, most solicited local and systemic AEs were Grade 1 or 2. No grade 3 solicited local AEs were reported in COV1001 and COV2001, although, a 2% of the participants reported a Grade 3 vaccination site pain in COV1002. The frequency of subjects with any Grade 3 solicited systemic AE in COV1001 was 9.9% in cohort 1a and 0.6% in cohort 3; it was a 7.8% in COV1002 and a 2.9% in COV2001.

Solicited AEs administered as 2-dose regimen

Safety data of a 2-dose regimen of Ad26.COV2.S ($5x10^{10}$ vp) administered at a 56-day interval was available from COV1001 in 77 adults ≥18 to ≤55 years (Cohort 1a) and 81 adults ≥65 years (Cohort 3) of age. In general, no safety concerns were identified after vaccination with two doses of Ad26.COV2.S ($5x10^{10}$ vp) at a 56-day interval, as no apparent difference was observed regarding the frequencies of solicited local and systemic AEs, and unsolicited AEs, when comparing a one dose and

two dose regimens, in adults aged ≥18 to ≤55 and aged ≥65. There were slightly higher frequencies of solicited systemic AEs after post-dose 1 than after post-dose 2. The main difference was regarding pyrexia. 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.

Unsolicited AEs

Study VAC31518COV3001

As defined in the protocol, for the participants in the safety subset, the investigator was to record systematically all unsolicited AEs, whether serious or non-serious from the time of vaccination until 28 days post-vaccination. Without such a requirement for a systematic collection of all unsolicited events for those participants in the FAS who were not in the safety subset (although spontaneous unsolicited reports were captured in the eCRF), and although a much larger number of subjects have been vaccinated with Ad26.COV2.S in FAS (21,895), the frequencies calculated in the safety subset (3,356 subjects vaccinated with Ad26.COV2.S) is preferred (higher than in the FAS). The selection of unsolicited AEs to be presented in the ADR table in the SmPC was made applying the following criteria (all criteria had to be met): Event occurred with a frequency of at least 0.1% in the safety subset; The AE was not collected as a solicited AE (to avoid duplication of the event in both solicited and unsolicited sections); The unsolicited AE occurred at a higher frequency (of >0.1%) in the Ad26.COV2.S group compared to the placebo group; A medical review was done to establish plausible connection to the vaccine and to assess confounding factors. Moreover, it has been checked that the unsolicited AEs reported in Ad26.COV2.S FAS (applying the same criteria as for the safety subset) are also present in the ADR table.

In the safety subset, the frequency of unsolicited AEs reported during the 28-days post-vaccination period was similar for participants in the Ad26.COV2.S group (13.1%) compared to participants in the placebo group (12%). In the Ad26.COV2.S group, the most frequently reported unsolicited AEs by PT (≥1.0% of participants) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. In the Ad26.COV2.S group, the unsolicited ADRs (not recorded as solicited AEs) selected for the ADR table in the SmPC are chills, arthralgia, malaise, asthenia, muscular weakness and pain in extremity (table below).

Table 31: Unsolicited Adverse Reactions Reported in the 28 Days Following Vaccination - Individuals 18 Years of Age and Older (Safety Subset COV3001)

ADVERSE REACTIONS	AD26.COV2.S N=3,356 N (%)	PLACEBO N=3,380 N (%)
CHILLS	67 (2.0%)	19 (0.6%)
ARTHRALGIA	35 (1.0%)	24 (0.7%)
MALAISE	26 (0.8%)	18 (0.5%)
ASTHENIA	18 (0.5%)	7 (0.2%)
MUSCULAR WEAKNESS	10 (0.3%)	5 (0.1%)
PAIN IN EXTREMITY	9 (0.3%)	3 (0.1%)

NOTE: SUBJECTS ARE COUNTED ONLY ONCE WITHIN A PERIOD FOR ANY GIVEN EVENT, REGARDLESS OF THE NUMBER OF TIMES THEY ACTUALLY EXPERIENCED THE EVENT IN THAT PERIOD. THE EVENT EXPERIENCED BY THE SUBJECT WITH THE WORST SEVERITY GRADE IS USED. IF A SUBJECT HAS MISSING SEVERITY GRADE FOR A SPECIFIC ADVERSE EVENT, THE SUBJECT IS COUNTED IN THE 'ANY' ROW FOR THAT ADVERSE EVENT.

Most reported unsolicited AEs were Grade 1 or Grade 2 in severity. There was as similar frequency of participants with unsolicited AEs of at least Grade 3 in both group (0.6% in the Ad26.COV2.S group vs. 0.5% in the placebo group).

The frequency of unsolicited AEs that were considered related to vaccination was higher in participants in the Ad26.COV2.S group (7.2%) compared to participants in the placebo group (4.6%) (table below).

There was an imbalance between vaccine and placebo in related unsolicited AEs (difference ≥ 2 related events in favour of vaccine group) observed for cough (12 related with vaccine vs. 4 in placebo), sneezing (10 vs. 8), oropharyngeal pain (5 vs. 1), tremor (3 vs. 1), back pain (3 vs. 1) and hyperhidrosis (2 vs. 0). These related events have been appropriately added in the ADR table in section 4.8 of the SmPC.

Table 32: Number of Subjects with Unsolicited Adverse Events Related to Vaccination (≥ 0.1% in Ad26 5e10 Group) by System Organ Class and Preferred Term; Safety Subset (Study VAC31518COV3001 – post-dose period)

	Ad26 5e10 (N = 3356) Number (%) of Participants	**Placebo (N = 3380)** Number (%) of Participants
Participants with 1 or more AEs	**242 (7.2%)**	**154 (4.6%)**
General disorders and administration site conditions	**173 (5.2%)**	**88 (2.6%)**
Chills	56 (1.7%)	8 (0.2%)
Fatigue	48 (1.4%)	48 (1.4%)
Vaccination site pain	41 (1.2%)	22 (0.7%)
Malaise	21 (0.6%)	6 (0.2%)
Asthenia	11 (0.3%)	5 (0.1%)
Vaccination site erythema	11 (0.3%)	7 (0.2%)
Vaccination site swelling	11 (0.3%)	2 (0.1%)
Pyrexia	8 (0.2%)	0
Injection site pain	7 (0.2%)	4 (0.1%)
Pain	3 (0.1%)	1 (<0.1%)
Musculoskeletal and connective tissue disorders	**52 (1.5%)**	**40 (1.2%)**
Myalgia	28 (0.8%)	31 (0.9%)
Arthralgia	16 (0.5%)	10 (0.3%)
Muscular weakness	5 (0.1%)	2 (0.1%)
Pain in extremity	4 (0.1%)	0
Back pain	3 (0.1%)	1 (<0.1%)
Nervous system disorders	**47 (1.4%)**	**44 (1.3%)**
Headache	38 (1.1%)	33 (1.0%)
Dizziness	3 (0.1%)	5 (0.1%)
Tremor	3 (0.1%)	1 (<0.1%)
Gastrointestinal disorders	**32 (1.0%)**	**34 (1.0%)**
Nausea	14 (0.4%)	20 (0.6%)
Diarrhoea	9 (0.3%)	8 (0.2%)
Odynophagia	5 (0.1%)	4 (0.1%)
Abdominal pain	4 (0.1%)	5 (0.1%)
Respiratory, thoracic and mediastinal disorders	**29 (0.9%)**	**18 (0.5%)**

Cough	12 (0.4%)	4 (0.1%)
Nasal congestion	10 (0.3%)	9 (0.3%)
Sneezing	10 (0.3%)	8 (0.2%)
Oropharyngeal pain	5 (0.1%)	1 (<0.1%)
Dyspnoea	3 (0.1%)	2 (0.1%)
Lower respiratory tract congestion	2 (0.1%)	0
Rhinorrhoea	2 (0.1%)	4 (0.1%)
Wheezing	2 (0.1%)	2 (0.1%)
Infections and infestations	**8 (0.2%)**	**11 (0.3%)**
Rhinitis	7 (0.2%)	7 (0.2%)
Skin and subcutaneous tissue disorder	**7 (0.2%)**	**4 (0.1%)**
Hyperhidrosis	2 (0.1%)	0
Metabolism and nutrition disorders	**5 (0.1%)**	**6 (0.2%)**
Decreased appetite	5 (0.1%)	6 (0.2%)
Eye disorders	**4 (0.1%)**	**1 (<0.1%)**
Eye irritation	2 (0.1%)	1 (<0.1%)
Eye pain	2 (0.1%)	0
Blood and lymphatic system disorders	**2 (0.1%)**	**2 (0.1%)**
Lymphadenopathy	2 (0.1%)	1 (<0.1%)
Investigations	**2 (0.1%)**	**1 (<0.1%)**
Body temperature increased	2 (0.1%)	0

Five subjects (0.1%) reported 6 unsolicited AEs of at least Grade 3 considered to be related to the study vaccine in the Ad26.COV2.S group (compared to 1 in placebo group): 1 chill, 1 fatigue, 1 malaise, 1 diarrhoea, 1 pain in extremity and 1 headache (none of grade 4) (table below).

Table 33: Number of Subjects With Unsolicited Adverse Events of at Least Grade 3 and Related to Vaccination by System Organ Class and Preferred Term; Safety Subset (Study VAC31518COV3001)

	Ad26 5e10	Placebo
Analysis set: Safety Subset	3356	3380
Post-Dose	3356	3380
Subjects with 1 or more AEs of at least grade 3 considered related to study vaccine	5 (0.1%)	1 (<0.1%)
General disorders and administration site conditions	3 (0.1%)	0
Chills	1 (<0.1%)	0
Fatigue	1 (<0.1%)	0
Malaise	1 (<0.1%)	0
Gastrointestinal disorders	1 (<0.1%)	0
Diarrhoea	1 (<0.1%)	0
Musculoskeletal and connective tissue disorders	1 (<0.1%)	1 (<0.1%)
Pain in extremity	1 (<0.1%)	0
Arthralgia	0	1 (<0.1%)
Nervous system disorders	1 (<0.1%)	1 (<0.1%)
Headache	1 (<0.1%)	0
Dizziness	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1%)
Nasal congestion	0	1 (<0.1%)
Sneezing	0	1 (<0.1%)
Wheezing	0	1 (<0.1%)

<u>Supportive studies (COV1001, COV1002 and COV2001)</u>

<u>Unsolicited AEs after dose 1</u>

In all studies, most solicited local AEs were Grade 1 or 2. No grade 3 unsolicited AEs (related or not) were reported with dose level $5x10^{10}$ vp of Ade26.COV2.S in COV1002 and COV2001. However, in COV1001, only 2 participants in each age group reported severe related unsolicited AEs.

<u>Unsolicited AEs administered as 2-dose regimen</u>

Safety data of a 2-dose regimen of Ad26.COV2.S ($5x10^{10}$ vp) administered at a 56-day interval was available from COV1001 in adults ≥18 to ≤55 years (Cohort 1a) and ≥65 years (Cohort 3) of age. There was no apparent difference in the frequencies of unsolicited AEs after vaccination with $5x10^{10}$ vp Ad26.COV2.S post-dose 1 compared to post-dose 2 in adults ≥18 to ≤55 years of age. There was slightly higher frequency of unsolicited AEs in participants who received $5x10^{10}$ vp Ad26.COV2.S. after dose 1 than after dose 2 in adults ≥65 years of age. Most unsolicited AEs were Grade 1 or 2 in severity. Lower frequencies of Grade 3 unsolicited AEs were observed after a second vaccination with Ad26.COV2.S in both age groups.

2.6.3. Immediate adverse events

In the main study COV3001, the first 2,000 participants in each of the 2 age groups (≥18 to <60 years and ≥60 years) remained under observation at the study site for at least 30 minutes after vaccination to monitor for immediate reactions. No early onset had been observed in either age group at the time of the Day 3 safety review of the initial 2,000 participants, therefore the observation period at the study site was reduced to at least 15 minutes for the remaining participants in the study. No anaphylactic or severe hypersensitivity reactions were observed immediately after vaccination (at the cut-off). Anxiety related reactions to vaccination, including vasovagal reactions such as syncope and presyncope, were rare (<0.1%) and evenly distributed amongst the Ad26.COV2.S and placebo groups. Immediate unsolicited reactions occurring within 30 minutes of vaccination were infrequent and occurred in 0.2% of participants in both the vaccine and placebo groups. There were 0.3% of participants with solicited reactions in in the Ad26.COV2.S group (0.3%) compared to participants in the placebo group (0.1%). None of the immediate events reported in the Ad26.COV2.S and placebo groups were considered serious. These findings are consistent with the safety data of the Ad26-vector platform.

2.6.4. Serious adverse event/deaths/other significant events

SAEs and deaths in pivotal study VAC31518COV3001

Deaths

Up to the cut-off date of 22 January 2021, fewer deaths were observed in the Ad26.COV2.S group (3 [<0.1%]) compared to the placebo group (16 [0.1%]) (table below). Out of the 16 deaths reported in the placebo group, 6 were confirmed to be associated with COVID-19. There were no deaths confirmed to be associated with COVID-19 in the Ad26.COV2.S group.

Table 34: Listing of Fatal Adverse Events; Full Analysis Set (Study VAC31518COV3001)

Vaccination Group	Preferred Term	COVID-19 Case as per clinical database	Day of AE Onset[a]	Duration (days)	COVID-19 Cases as per Janssen WHO clinical assessment [b]
Ad26.COV2.S $5x10^{10}$ vp	Death		45	1	Not COVID-19
	Lung abscess[c]		33	27	Not COVID-19
	Pneumonia[c]		11	14	Not COVID-19
Placebo	Completed suicide		25	1	Not COVID-19
	Acute myocardial infarction		62	1	Not COVID-19
	Death		25	1	Not COVID-19
	Death		41	1	Not COVID-19
	Pneumonia		59	3	Not COVID-19
	Accidental overdose		7	1	Not COVID-19
	Sudden death		58	1	Not COVID-19
	COVID-19	Yes	25	14	Confirmed COVID-19
	Cardiac failure	Yes	15	1	Confirmed COVID-19
	Pneumonia		27	2	Probable COVID-19
	Malaise		.	.	Not COVID-19
	COVID-19	Yes	32	8	Confirmed COVID-19
	Suspected COVID-19		23	4	Probable COVID-19

Vaccination Group	Preferred Term	COVID-19 Case as per clinical database	Day of AE Onset[a]	Duration (days)	COVID-19 Cases as per Janssen WHO clinical assessment [b]
	COVID-19 pneumonia[d]	Yes (PCR positive at baseline)	10	9	Confirmed COVID-19
	COVID-19	Yes	28	4	Confirmed COVID-19
	COVID-19 pneumonia	Yes	46	10	Confirmed COVID-19

Key: AE = adverse event
[a] Day of AE Onset is in reference to the date of first vaccination.
[b] WHO COVID-19: Case Definitions, published 16 December 2020.
[c] Had a negative COVID-19 test result indicated in CIOMS form.
[d] Had a positive PCR result at baseline.
Note: Adverse events are coded using MedDRA Version 23.0.

All 3 deaths reported in the Ad26.COV2.S group were assessed by the investigator as not related: fatal SAE of lung abscess co-reported with AEs of chest pain, cough, and vomiting in 42 years of age male with a TTO of 32 days, case maybe confounded by underlying condition; negative COVID-19 test result), fatal SAE of pneumonia (reported in 61 years of age female with a TTO of 11 days, negative COVID-19 test result; without any other explanatory factors, the relation of the death to the vaccine cannot be excluded), and 1 death of unknown cause at the time of data cut-off (in 66 years of age female with a TTO of 44 days, insufficient information to perform a causality assessment, but in the absence of reactogenicity symptoms and long time to onset, the event is considered not related by the applicant).

Serious adverse events

Overall, 90 [0.4%] subjects in the Ad26.COV2.S group and 137 [0.6%] subjects in the placebo group reported 1 or more SAEs. However, a total of 83 (0.4%) subjects reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared to 96 (0.4%) subjects in the placebo group. SAEs associated with COVID-19 were reported in the infections and infestations and in the investigations (SARS-CoV_2 test positive) SOCs (system organ class).

A total of 8 (<0.1%) participants reported SAEs associated with COVID-19 in the Ad26.COV2.S group compared to 44 (0.2%) participants in the placebo group. Among the SAEs not associated with COVID-19, overall, no major imbalances were observed by SOC. The most frequently reported SAEs by SOC in the Ad26.COV2.S and placebo groups were infections and infestations (0.1% [23 participants] in the Ad26.COV2.S group and 0.1% [27 participants] in the placebo group) and nervous system disorders (< 0.1% [10 participants] in the Ad26.COV2.S group and 0.1% [8 participants] in the placebo group).

Treatment related SAEs

Nine participants reported a total of 10 SAEs (7 in the Ad26.COV2.S group and 3 in the placebo group) which were considered to be related to the study vaccine by the investigator. The 7 related SAE reported by 7 subjects in the Ad26.COV2.S group were Grade 4 Guillain-Barré syndrome, Grade 3 radiculitis brachial, Grade 3 post-vaccination syndrome (asthenia), two Grade 2 facial paralysis (Bell's Palsy), Grade 4 pericarditis and Grade 3 hypersensitivity (angioedema).

Medical attended adverse events

MAAEs were reported for all participants from the moment of vaccination until 6 months after the vaccination, except for MAAEs leading to study discontinuation, which were to be reported during the entire study.

Up to the cut-off date , 304 (1.4%) participants reported one or more MAAEs in the Ad26.COV2.S group compared to 408 (1.9%) participants in the placebo group. Overall, no major imbalances were observed by SOC. The most frequently reported MAAEs by SOC in the COVID-19 vaccine and placebo groups were infections and infestations.

SAEs and deaths in supportive studies (VAC31518COV1001, VAC31518COV1002, VAC31518COV2001 and VAC31518COV3009)

Overall, safety data on deaths, SAEs, and AEs leading to study discontinuation are available from supportive clinical studies COV1001, COV1002, COV2001 and COV3009. As most of the data is still blinded, the data reported is aggregated and not divided between the vaccine and placebo groups. The studies include >10,500 participants ≥18 years of age who received either placebo or active vaccine at doses up to $1x10^{11}$ vp. In the supportive studies, up to the cut-off date of 11 January 2021 (COV1001, COV1002, and COV2001) and 14 January 2021 (COV3009), 1 non-related death was reported, and few SAEs were observed. Early discontinuations of vaccination or study due to (S)AEs were infrequent in all groups. A total of 26 participants reported 1 or more SAEs. Of these, 2 SAEs were considered to be related to the study vaccine. In COV1001, a Grade 3 SAE pyrexia was reported post dose 1 of the Ad26.COV2.S vaccine ($1×10^{11}$ vp) and led to discontinuation of further vaccination. A multiple sclerosis event was reported during follow-up post-dose 1 in study COV1001 for a participant who received placebo that led to discontinuation of further vaccination. This SAE was considered related to the intervention by the investigator but was considered chronic and preceding vaccination by an expert neurologist. In addition, 7 SAEs considered unrelated and 18 nonserious AEs consisting primarily of COVID-19 infections led to discontinuation of the vaccine or study.

2.6.5. Adverse Events of Interest

In COV3001, as, per protocol, there were no pre-specified AESIs for Ad26.COV2.S clinical development, the applicant followed a dynamic medical review of incoming AEs to identify potential safety issues. Up to the cut-off date , in the FAS, 140 (0.6%) participants reported at least one treatment emergent AESI in the Ad26.COV2.S group compared to 134 (0.6%) participants in the placebo group. Few reported AESIs were assessed as related: 0.2% in the Ad26.COV2.S group compared to 0.1% participants in the placebo group. For the majority of the reported AESIs, because of lack of plausible biological mechanism, too long time to onset, alternative explications (such as underlying pathologies) and confounding factors, causality could not be clearly established.

Allergic reactions

In study COV3001, the most frequently reported AEs in the broad SMQ 'non-anaphylactic allergic reactions' (≥6 participants in the Ad26.COV2.S group) were rash (24 participants active vaccine including 10 assessed as relate, 16 placebo including 6 related), urticaria (8 participants active vaccine including 3 related, 3 placebo – none related), and hypersensitivity (6 participants active vaccine including 1 related, 4 placebo – none related).

Hypersensitivity, rash, urticaria and anaphylaxis have been identified as ADRs in the SmPC. Anaphylaxis has been included as an important identified risk in the list of safety concerns of the RMP.

Immune-mediated neurological disorders

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

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

Other Nervous system disorders

A numerical imbalance observed between the Ad26.COV2.S group and placebo group for:

- Tinnitus: Six cases of tinnitus were reported in the Ad26.COV2.S group and none in the placebo group. For these events, a causal relationship with the Janssen COVID-19 vaccine cannot be determined. The assessment of causality was confounded by the presence of underlying medical conditions that could have contributed to these events.

- Convulsions/seizures: Four cases were reported in the Ad26.COV2.S group (1 serious) and one case (non-serious) in the placebo group, all of which were considered not related to the study vaccine by the investigator. The risk of generalised convulsion is included in the list of AESIs taken in consideration for routine and additional pharmacovigilance activities.

Injection site bruising

There were 22 subjects with haemorrhagic disorders in the Ad26.COV2.S group compared to 25 in the placebo group. An appropriate warning has been specified in SmPC section 4.4 (i.e. 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).

Thromboembolic disorders

A numerical imbalance was observed for the venous thromboembolic events with 11 subjects in the vaccine group vs. 4 in the placebo group. In the vaccine group, there were: 6 DVT type events, 4 pulmonary embolism, 1 transverse sinus thrombosis (including 6 SAEs & 1 non-serious related AE; 8 events occurred within 28 days following vaccination). In the placebo group, there were: 2 DVT events, 1 pulmonary embolism, 1 thrombosed haemorrhoid (including 1 related SAE & 1 none-related SAE, all within 28 days of vaccination). The majority of the participants had underlying medical conditions (such as obesity, hypothyroidism, diabetes) that could have contributed to the thrombotic and thromboembolic events. Only 1 SAE of DVT was reported with Ad26 vaccine (in adult FAS after 28 days after vaccination) in AdVac report V5. Venous thromboembolism has been included as an important potential risk in the list of safety concerns of the RMP.

Respiratory disorders

AE of asthma was reported for 7 participants in the Ad26.COV2.S group versus 1 participant in the placebo group. For the majority of the participants (including the participant in the placebo group), the assessment of "not related" was made considering the nature of the condition and the subject's medical history (including longstanding history of asthma).

In the Respiratory, thoracic and mediastinal disorders, 10 subjects reported 10 SAEs in the COVID-19 group (3 Pulmonary embolism, 2 Dyspnoea, 2 Hypoxia, 1 Chronic obstructive pulmonary disease, 1 Pleural effusion, 1 Pneumothorax spontaneous) compared to 4 subjects reporting 6 SAEs in the placebo group (Pulmonary embolism, Dyspnoea, Cough, Oropharyngeal pain, Respiratory distress, Respiratory failure).

Although the causality is not clear, because there is an imbalance, the risk of exacerbation of chronic pulmonary disorders (i.e. asthma and COPD) might be further monitored in the planned PASS if feasibility is confirmed.

Increased HIV acquisition risk

The risk for increased HIV acquisition after vaccination with Ad26-based vaccines is considered to be theoretical. In the AdVac Safety Database V5.0, there were 3 cases of incident HIV infection in Ad26-vaccinated individuals in HIV-V-A004, all captured as SAEs from the same site, which is situated in a high endemic region for HIV infection (all cases presenting risk factors for HIV infection) (compared to none in the placebo group). To date, there were no incident HIV infections reported in clinical studies with Ad26.COV2.S. The applicant has been recommended to submit the next version of the Adenoviral Vaccine Safety Database (V6.0) including a discussion of the potential increased risk of HIV acquisition in individuals vaccinated with adenovirus-based vaccines with a review of reported cases in the updated Ad26 platform data (expected for approximatively April 2021) (see list of recommendations).

2.6.6. Laboratory findings

Clinical laboratory evaluations were only conducted in COV1001, COV1002 (blinded), and COV2001 (blinded). Overall, a low number of laboratory abnormalities were reported as an AE after vaccination with Ad26.COV2.S.

In study COV1001 Cohort 1a, laboratory abnormalities were reported as AEs (Grade 1 or 2 in severity), in the active vaccine groups but no risk minimisation procedures were considered needed. Examination of safety laboratory assessments at the different timepoints for all vaccination groups showed no notable differences compared with baseline values and/or with values from the placebo group. Overall, the percentages of participants with abnormal safety laboratory values (biochemistry, haematology, coagulation, and urinalysis) were very low and no differences were noted between vaccine and placebo groups, vaccine dose levels, and first versus second dose. In study COV1002 at the time of the interim analysis, one laboratory-related AE was reported in a participant in the placebo group with Grade 1 C-reactive protein increased 15 days after the first vaccination. The AE was considered not serious and not related to vaccination. The event resolved by the next measurement which occurred 18 days later. In study COV2001, no laboratory-related AEs were reported post-dose 1. Individual laboratory data at the different timepoints were not available at the time of this analysis.

Vital signs measurements included body temperature, pulse/heart rate, respiratory rate, and blood pressure. Overall, a low number of vital sign-related AEs were observed after vaccination with Ad26.COV2.S.

In study COV1001 the following vital signs-related AEs were reported: one Grade 3 AE of hypotensive crisis after vaccination which was considered related to the study vaccine by the investigator and one serious Grade 3 AE of decreased blood pressure, one Grade 2 AE of bradycardia, one Grade 2 and one Grade 1 AE of syncope and one Grade 1 AE of hypertension, all of them after vaccination and which were considered unrelated to the study vaccine by the investigator. The event of hypotensive crisis occurred immediately after vaccination and coincided with an anxiety reaction and the applicant is, therefore, of the opinion that the event of hypotensive crisis was anxiety related. As anxiety-related

reactions post vaccination are listed in the warnings and precautions section of the SmPC and based on the described vital signs-related AEs, no additional risk minimisation procedures are considered needed.

While looking at the Emerging worst vital signs abnormalities in COV1001, frequencies of subjects with abnormalities (bradycardia, hypertension, hypotension, and tachycardia) were comparable in the different groups (active vaccine groups or placebo group). Only the respiratory rate seems increased post-dose 1 in the 5×1010 vp Ad26.COV2.S / 5×1010 vp Ad26.COV2.S group (19.5%) compared to PL/PL group (11.7%). This difference is not seen post-dose 2.

In study COV1002 at the time of the interim safety analysis for Cohort 1 one vital signs-related AE of presyncope was reported in a participant who received Ad26.COV2.S at $5x10^{10}$ vp.

In COV2001, a total of 4 participants in the Ad26.COV2.S (2 participants in the Ad26.COV2.S $5x10^{10}$ vp [0.7%] and 2 in the 1x1011 vp [2.7%] group) were reported with hypertension. Overall, 3 participants (all reported in the Ad26.COV2.S 5x1010 vp [1.1%] group) were reported with pyrexia and 2 participants (1 participant in the Ad26.COV2.S $5x10^{10}$ vp [0.4%] and 1 in the $1x10^{11}$ vp [1.4%] group) were reported with syncope. Other AEs (PTs) occurred in at most 1 participant in the combined Ad26.COV2.S groups. No vital signs-related AEs were reported in the placebo group. No Grade 3 vital signs-related AEs were reported.

In study COV3001, up to 28 days post vaccination, 14 (0.4%), 7 (0.2%) and 4 (0.1%) of the participants (safety subset) in the Ad26.COV2.S group were reported with pyrexia, hypertension and syncope, respectively, versus 5 (0.1%), 2 (0.1%) and 5 (0.1%) participants, respectively in the placebo group. Other AEs (PTs) were reported in at most 1 participant in the Ad26.COV2.S group and/or the placebo group. No Grade 3 vital sign-related AEs were observed after vaccination with Ad26.COV2.S. Two Grade 3 hypertension AEs were reported after vaccination with placebo which were considered unrelated to the study vaccine.

In COV3009, overall, blinded data (FAS; AEs up to 28 days after the first vaccination) were in line with the observations in COV3001 with the most frequently reported vital signs-related AEs being pyrexia (25 [0.3%] participants overall) and syncope (3 [<0.1%] participants overall). Other AEs (PTs) were reported in at most 2 participants overall.

2.6.7. Safety in special populations

The safety parameters were reviewed by subgroup for age at randomisation, comorbidity at baseline, by Region, by gender, baseline serostatus and HIV infection. Overall, the safety profile of Ad26 5x1010 was generally similar independently of the subgroups, in particular the frequencies of subjects with SAEs, MAAEs and AESIs (rare). In the Ad26 5x1010 group, for all subgroups, most solicited AEs were Grade 1 or Grade 2 in severity, and most solicited AEs were transient in nature and reported as resolved. The nature of the local and systemic AEs recorded was similar, showing the same pattern as for the pooled population.

2.6.7.1. Age groups

Main clinical study: VAC31518COV3001

Overall, the demographic and baseline characteristics were consistent between these age subgroups. However, not surprisingly, in the Ad26 $5x10^{10}$ group (safety subset), there were less comorbidities at baseline in the younger group (31% for subjects 18 to 64 years of age), compared to the older group (45% for subjects ≥65 years of age).

In the Ad26 5x10[10] group the frequency of subjects with solicited local AEs clearly decreases with age 55.7% for subjects aged ≥18 to 64 vs. 31.8% for subjects aged ≥65 years. This lower frequency in participants aged ≥65 years was reported for all selected solicited local AEs, including the most frequent solicited local AE, ie, vaccination site pain: 54.3% in subjects aged ≥18 to 64 (86% grade 1, 13.4% grade 2, 0.6% grade 3) vs. 29.6% in subjects aged ≥65 years (94.3% grade 1, 4.4% grade 2, 1.3% grade 3).

The frequency of subjects with solicited systemic AEs also clearly decreases with age: 59.6% for subjects aged ≥18 to 64 vs. 40.2% for subjects aged ≥65 years. A higher frequency was reported for all selected solicited systemic AEs (fatigue, headache, myalgia, nausea, and pyrexia) in younger subjects. In particular, there were 11% subjects aged ≥18 to 64 years with pyrexia compared to 2.4% subjects aged ≥65 years.

In the Ad26 5x10[10] group, for all the 2 age subgroups, most solicited AEs were Grade 1 or Grade 2 in severity. There were slightly more grade 1 solicited local and systemics AEs in subjects aged ≥65 years compared to subjects aged ≥18 to 64, and less grade 2 solicited local and systemics AEs.

Table 35 Adverse Events (MedDRA Terms) for Elderly Participants (Study VAC31518COV3001)

		Ad26 5e10				**Placebo**			
MedDRA Terms		**Age <60 y**	**Age 60-69 y**	**Age 70-79 y**	**Age 80+ y**	**Age <60 y**	**Age 60-69 y**	**Age 70-79 y**	**Age 80+ y**
	Population / Period	**Number (Percentage)**	**Number (Percentage)**	**Number (Percentage)**	**Number (Percentage)**	**Number (Percentage)**	**Number (Percentage)**	**Number (Percentage)**	**Number (Percentage)**
Total AEs	Safety Subset / Post Dose	285 (14.0%)	114 (12.4%)	36 (10.1%)	5 (12.5%)	275 (13.4%)	93 (9.7%)	35 (10.5%)	4 (10.5%)
	FAS/ Entire Study (N)	**14,564**	**5,224**	**1,893**	**214**	**14,547**	**5,362**	**1,762**	**217**
Serious AEs – Total	FAS/ Entire Study	50 (0.3%)	25 (0.5%)	14 (0.7%)	1 (0.5%)	69 (0.5%)	42 (0.8%)	21 (1.2%)	5 (2.3%)
- Fatal	FAS/ Entire Study	1 (<0.1%)	2 (<0.1%)	0	0	7 (<0.1%)	7 (0.1%)	2 (0.1%)	0
- Hospitalisation/prolong existing hospitalisation	FAS/ Entire Study	42 (0.3%)	22 (0.4%)	13 (0.7%)	1 (0.5%)	60 (0.4%)	35 (0.7%)	21 (1.2%)	3 (1.4%)
- Disability/incapacity	FAS/ Entire Study	1 (<0.1%)	1 (<0.1%)	0	1 (0.5%)	7 (<0.1%)	1 (<0.1%)	1 (0.1%)	0
- Other (medically significant): MAAE	FAS/ Entire Study	207 (1.4%)	68 (1.3%)	26 (1.4%)	3 (1.4%)	272 (1.9%)	84 (1.6%)	43 (2.4%)	9 (4.1%)
AE leading to study discontinuation	FAS/ Entire Study	0	0	0	0	0	0	0	0
	Safety Subset / Post Dose (N)	**2,036**	**923**	**357**	**40**	**2,049**	**961**	**332**	**38**
Psychiatric disorders	Safety Subset / Post Dose	3 (0.1%)	2 (0.2%)	0	0	9 (0.4%)	0	0	0
Nervous system disorders	Safety Subset / Post Dose	72 (3.5%)	20 (2.2%)	6 (1.7%)	0	69 (3.4%)	30 (3.1%)	9 (2.7%)	0
Accidents and injuries SMQ broad	Safety Subset / Post Dose	7 (0.3%)	4 (0.4%)	0	0	7 (0.3%)	3 (0.3%)	0	1 (2.6%)
Cardiac disorders	Safety Subset / Post Dose	0	1 (0.1%)	1 (0.3%)	0	1 (<0.1%)	0	0	0
Vascular disorders	Safety Subset / Post Dose	6 (0.3%)	2 (0.2%)	2 (0.6%)	0	3 (0.1%)	1 (0.1%)	1 (0.3%)	0
Cerebrovascular disorders, Central nervous system vascular disorders SMQ broad	Safety Subset / Post Dose	1 (<0.1%)	0	0	0	0	0	0	0

Infections and infestations	Safety Subset / Post Dose	42 (2.1%)	10 (1.1%)	4 (1.1%)	1 (2.5%)	60 (2.9%)	16 (1.7%)	9 (2.7%)	2 (5.3%)
Anticholinergic syndrome: broad SMQ	Safety Subset / Post Dose	18 (0.9%)	5 (0.5%)	1 (0.3%)	0	9 (0.4%)	5 (0.5%)	2 (0.6%)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia	Safety Subset / Post Dose	14 (0.7%)	6 (0.7%)	1 (0.3%)	0	10 (0.5%)	6 (0.6%)	2 (0.6%)	1 (2.6%)

AE = adverse event; FAS = Full Analysis Set; MAAE = medically-attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query; y = years;

2.6.7.2. Co-morbidities

In the safety subset of main trial COV3001, the frequencies of subjects with local and systemic solicited AEs decrease for subjects with baseline comorbidities compared to subjects without baseline comorbidities in the Ad26.COV2.S group only (differences not observed in the placebo group):

- The frequency of solicited local AEs was lower in participants with one or more comorbidities (42.9%) compared to participants without comorbidities at baseline (54%).

- Solicited systemic AEs were reported less frequently in participants with one or more comorbidities (49.6%) compared to participants without comorbidities at baseline (58.1%).

Subjects 18-64 years of age with comorbidities at baseline shows less local solicited AEs than the subjects 18-64 years of age without comorbidities, and less systemic solicited AEs than the subjects 18-64 years of age without comorbidities. Subjects from 65 years of age with comorbidities at baseline shows similar reactogenicity than the subjects from 65 years of age without comorbidities.

No specific concerns arise in the observed safety profile so far.

2.6.7.3. Use in pregnancy and lactation

Up to the cut-off date of 31 December 2020, 8 pregnancies were reported in the GMS database for study COV3001: 4 in COVID-19 vaccine group and 4 in placebo group. In the COVID-19 group, 2 pregnancies were still ongoing, and there were 1 spontaneous abortion and 1 ectopic pregnancy (both assessed as not related to vaccine). In the placebo group, 1 pregnancy was still ongoing, and there were 1 incomplete abortion and 2 elective abortions. Although, up to the cut-off date of 31 December 2020, 285 breastfeeding women (128 in Ad26.COV2.S group and 157 in placebo group) were enrolled, no further information regarding breastfeeding was requested during the study.

Use during pregnancy and in breastfeeding women are considered as missing information in the RMP.

2.6.7.4. By Region

In the safety subset of the main trial COV3001, the frequencies of subjects with local and systemic solicited AEs were slightly higher in Northern America compared to Latin America and Southern Africa in the Ad26.COV2.S group only (differences not observed in the placebo group).

2.6.7.5. By gender

In the Ad26 $5x10^{10}$ group (FAS) regarding the main trial COV3001, there were 12,071 males (55.1%) and 9,820 females (44.9%).

In the safety subset, the frequencies of subjects with local and systemic solicited AEs were higher in females compared to males in the Ad26.COV2.S group only (differences not observed in the placebo group):

- In the Ad26.COV2.S group, the frequency of local solicited AEs was higher in female (54.5%) compared to males (46.2%).

- In the Ad26.COV2.S group, the frequency of systemic solicited AEs was also higher in female (59.9%) compared to males (50.7%)

No major differences are observed for the grade 3 local solicited events (1% in females vs. 0.4% in males).

2.6.7.6. By baseline Serostatus

In the Ad26 $5x10^{10}$ group (FAS) regarding main trial COV3001, there were 2,151 subjects (9.8%) seropositive at baseline and 19,744 subjects (90.2%) seronegative at baseline (respectively, 2,066 subjects (9.4%) and 19,822 subjects (90.6%) in placebo group). Overall, the safety profile of Ad26 $5x10^{10}$ was generally similar in adults seropositive and seronegative at baseline for SARS-CoV-2. The nature of the local and systemic AEs recorded was similar, showing the same pattern as for the pooled population, without any clinically meaningful differences in frequencies. However, the number of vaccinated subjects who were seropositive at baseline is too limited in the safety subset to draw any definitive conclusions.

No specific concerns arise in the observed safety profile so far.

2.6.7.7. By HIV infection

In the main trial: COV3001, there were 601 subjects (2.7%) HIV infected at baseline and 8,335 subjects (38.1%) not HIV infected at baseline vaccinated with Ade26.COV2.S. No safety concern was observed in adults with stable/well-controlled HIV infection who received the COVID-19 Vaccine Janssen

Nevertheless, the number of vaccinated subjects HIV infected at baseline is too limited in the safety subset to draw any conclusions regarding reactogenicity (34 in Ad26.COV2.S group and 25 in placebo group). Use in immunocompromised patients is identified as a missing information in the RMP.

2.6.7.8. By dose level

Supportive Clinical Studies (COV1001, COV1002, COV2001)

Safety data from Ad26.COV2.S administered at different dose levels are available from COV1001 ($5x10^{10}$ vp and $1x10^{11}$ vp) and COV2001 ($1.25x10^{10}$ vp, $2.5x10^{10}$ vp, $5x10^{10}$ vp, and $1x10^{11}$ vp) in adults ≥18 to ≤55 years and ≥65 years of age and from COV1002 ($5x10^{10}$ vp and $1x10^{11}$ vp) in adults ≥20 to ≤55 years of age. Safety data up to 28 days post dose 1 for each study are described below. For COV1001 and COV2001, data post dose 1 were pooled within each cohort by dose level within each study.

Overall, no safety concerns were identified after vaccination with Ad26.COV2.S at dose levels up to $1x10^{11}$ vp. The available safety data are supportive of the dose selection for the Phase 3 studies.

2.6.8. Immunological events

Refer to AESIs for an overview of immunological events.

2.6.9. Safety related to drug-drug interactions and other interactions

Interaction with another vaccine was not studied. Interaction with other vaccines is identified as a missing information in the RMP.

Antipyretics/analgesics were recommended post-vaccination for symptom relief as needed. In FAS, a similar frequency of subjects used corticosteroids in both group (2.8% in Ad26.COV2.S vs. 2.7% in placebo).

In the safety subset, a higher percentage of participants in the Ad26.COV2.S group than the placebo group used antipyretics/analgesics in this period (19.9% and 5.7% of participants, respectively).

The frequencies of subjects with local and systemic solicited AEs were clearly lower in subjects who did not used antipyretics / analgesics (A/A) post-vaccination compared to those who used A/A in the Ad26.COV2.S group (and also for the grade 3 solicited AEs):

The frequencies of subjects with solicited AEs were slightly lower in subjects who did not used corticosteroids compared to those who used corticosteroids in the Ad26.COV2.S group

2.6.10. Discontinuation due to adverse events

In study COV3001: For all participants, all SAEs, AEs and MAAEs leading to study discontinuation were to be reported until completion of the participants last study-related procedure. No AEs or MAAEs resulting in study discontinuation were reported.

Up to the cut-off date of 11 January 2021 (COV1001, COV1002, and COV2001) and 14 January 2021 (COV3009): In COV1001, 3 unsolicited AEs resulted in study vaccine discontinuation: 1 Grade 3 SAE of pyrexia reported post-dose 1 in the 1×10^{11} vp active vaccine (considered related to the study vaccine by the investigator), 1 Grade 1 AE of COVID-19 reported post-dose 1 in the 1×10^{11} vp, (considered not related to study vaccine); 1 Grade 2 SAE of multiple sclerosis reported in post-dose 1 follow-up in the placebo group). One SAE of nephrolithiasis (Grade 4) was reported during post-dose 1 follow-up for a participant who received active vaccine at the $5x10^{10}$ vp dose level which led to discontinuation of further vaccination (considered unrelated to the study vaccine by the investigator – acknowledged: past medical history of kidney stones etc…). In COV1002, there were 3 discontinuations due to SAEs (2 blood pressure increased, 1 dizziness postural – all not related) with blinded vaccine. In COV2001, there were 3 discontinuations due to SAEs (not related lung adenocarcinoma and related parasthesia) with blinded vaccine. In COV3009, there were 3 discontinuations due to SAEs (couch, delirium and pleuritic pain – all not related) with blinded vaccine.

2.6.11. Post marketing experience

No data available as Ad26.COV2.S has just been authorised through EUA in the USA since 28 February 2021.

2.6.12. Supportive clinical safety data of vaccine using the Ad26 Vector

As of 04 September 2020, different Ad26 platform-based vaccines developed by Janssen have been administered to 114,174 participants. Safety data are available from six reports: AdVac safety database report V5.0 (4,874 participants enrolled as of the data cut-off date of 20 December 2019), additional reviews of individual case safety reports of SAEs and pregnancy exposures (up to 31 October 2020; cases which were not part of the current AdVac report), complete cumulative reviews of SAEs and pregnancy cases (up to the cut-off of 21 December 2020), and complete cumulative review of neuroinflammatory AEs (up to the cut-off of 21 January 2021).

Data from the AdVac safety database report V5.0 supported the accelerated development of the vaccine candidate Ad26.COV2.S for the prevention of COVID-19, including the dose levels used in the FIH.

Most of the data are from the Ebola programme. Significant amount of data is also available from the RSV and HIV programme. Data for other inserts are very limited. The majority of enrolled individuals were healthy, Black or African American, or White. Imbalance between groups observed in the AdVac safety database V5 (in particular, for region and ethnicity) should be explained and the impact on the results should be discussed (see list of recommendations).

Baseline seropositivity to Ad26 was evaluated in the three large Janssen Vaccines' clinical vaccine programs (Ebola, HIV, and RSV) across various geographic locations and in varying study populations (n=3851). Ad26 seroprevalence varied by continent, with the highest seroprevalence reported in Africa (77.9% [95% CI 75.9;79.7],n=1,872), followed by Asia (41.4% [28.9;55], exclusively in Thailand, n=58), and comparatively low seroprevalence levels in North America (15.1% [13.5;16.9], exclusively USA, n=1,748), and Europe (11.6% [7.4;17.5], n=173). To assess the influence of natural pre-existing immunity to Ad26 on humoral responses, a cross-study analysis was performed by assessing insert-specific Ab specifically post 1 Ad26-based vaccination. Based on the limited data, it is considered that an impact of pre-existing anti-Ad26 vector immunity on insert specific vaccine-elicited immune responses cannot be excluded. The applicant has also presented the first data obtained in the COVID-19 program to further document this potential impact of immunity to Ad26. However, the data gathered so far do not allow the assessment of the impact of natural pre-existing anti-Ad26 vector immunity since only 2 subjects had Ad26 nAb at baseline. Of importance, the data of COVID-19 program so far do not indicate an apparent negative impact of anti-Ad26 vector immunity induced by the first vaccine dose on the insert specific vaccine-elicited humoral immune responses post-dose 2. The impact on T cell responses was not presented. The potential impact of natural or vaccine induced pre-existing anti-Ad26 immunity on vaccine efficacy remains unclear and should be further documented. Further data are expected with the COVID-19 program and would help to better characterise the impact of natural and vaccine-induced Ad26 immunity on the antigen specific vaccine-induced immune responses, and its possible impact on vaccine efficacy (see list of recommendations).

In healthy younger adults (18-60-year-old), overall, Ad26-based vaccines were well tolerated, irrespective of the insert, the dose level and the dose number; however, safety data have been provided irrespective of dose levels and per subject (cumulating AE after all doses). In next Advac reports, the applicant is recommended to provide the solicited AE separately for dose level $5x10^{10}$ (relevant for the COVID-19 vaccination) and other dose levels, and, separately, after dose 1 and after dose 2 (compared to placebo) (see list of recommendations).

Several factors could influence reactogenicity (age, region, pre-existing immunity to Ad26, antigen insert, and dose level). In particular, it has been observed that:

The frequencies (per subject) of local solicited AEs following Ad26 was slightly higher in the younger age category (64.0% of adults aged 18-30 years) compared to the 31-50 years and ≥50 years (56.5%

and 57.2% respectively). The frequencies of systemic solicited AEs following Ad26 was also higher in the younger age category (73.5% of adults aged 18-30 years) compared to the 31-50 years and ≥50 years (62.9% and 62.3% respectively).

The frequency of solicited AE local and systemic is generally much lower in West Africa than in other regions (East and Southern Africa, North America, Europe, and Asia), both for the active and placebo groups. Discrepancies across regions could also reflect differences in terms of pre-existing immunity to Ad26 (higher in Africa) and methodological differences between studies. This should be discussed in the next Advac report (see list of recommendations).

Overall, the frequency of solicited local (most notably injection site pain) and systemic AEs (mostly headache, fatigue, myalgia, and chills) tended to be lower in individuals with pre-existing Ad26 neutralising antibody titres (Ad26 VNA positivity at baseline) compared to individuals without pre-existing Ad26 neutralising antibody titres at baseline. This was observed for Zabdeno (EPAR) and confirmed by the cross-study analysis summarised in the report 'Influence of Natural Pre-existing Immunity to Ad26 on Humoral Immune Responses post 1 Ad26-based Vaccination' (Ebola and HIV programmes). The cross-study analysis indicated that the association remained when stratifying by continent. This observation is unlikely to impact the use of the vaccine. The independent effect of pre-existing immunity to the vector on reactogenicity remains not fully clear.

For the inserts that have been tested in more than 100 subjects, high differences of frequency of solicited local and systemic AE (all grade and severe – related to vaccine or not) have been reported depending on the insert. These differences are difficult to interpret given the confounding effect of study location (Africa vs other regions), age distribution, and dose level used. Hence, the independent effect of the insert on reactogenicity remains unclear. This should be discussed in a next Advac report, based on more detailed stratified analyses (see list of recommendations).

It is difficult to establish an effect of dose level, as relatively few individuals received Ad26 doses of 1×10^9 vp, 1×10^{10} vp, and 9×10^{10} vp. When only groups with more than 100 individuals were considered (0.8×10^{10} vp, 2×10^{10} vp, 5×10^{10} vp, and 1×10^{11} vp dose levels), there was a trend towards an increase in the frequency of some local solicited AEs (all grade and severe, in particular injection site pain), and solicited systemic AEs (all grade and severe, and considered related to study vaccine, in particular arthralgia, chills, fatigue, headache, myalgia, and nausea), following the increase in Ad26 dose. There was no clear trend in the frequency of unsolicited AEs with increasing the Ad26 dose.

An increased risk of HIV acquisition in individuals vaccinated with adenovirus-based vaccines is considered as an important potential risk. This safety concern has been raised with an Ad5-vectored HIV vaccine. An increased risk of HIV-1 acquisition was observed in subjects vaccinated with an experimental Ad5-vectored HIV vaccine compared to control subjects (Buchbinder *et al*., 2020). It was hypothesised that activated Ad5-specific CD4 T cells could increase rates of HIV-1 acquisition. Although the association between risk of HIV-1 acquisition and Ad5-based (or other Ad-based) vaccines is controversial and the mechanism for increased risk is unclear, this potential risk should be taken into account in studies with this viral vector platform. The overall assessment of the risk for increased HIV acquisition after vaccination with Ad26-based vaccines is considered to be theoretical. In the AdVac Safety Database V5.0, there were 3 cases of incident HIV infection in Ad26-vaccinated individuals in HIV-V-A004, all captured as SAEs from the same site, which is situated in a high endemic region for HIV infection (all cases presenting risk factors for HIV infection) (compared to none in the placebo group). In study VAC52150EBL2002 (Ebola vaccine), one adult male participant tested HIV seropositive approximately 1 year after receipt of one dose of Ad26.ZEBOV (sexually inactive at study enrolment; no further information available about risk factors for HIV infection). There have been no HIV infections reported in the development programs of RSV, Filovirus, and malaria Ad26-vectored

vaccines. To date, there were no incident HIV infections reported in clinical studies with Ad26.COV2.S. The next version of the Adenoviral Vaccine Safety Database (V6.0) should be submitted including a discussion of the potential increased risk of HIV acquisition in individuals vaccinated with adenovirus-based vaccines with a review of reported cases in the updated Ad26 platform data (expected for approximatively April 2021). (see list of recommendations)

Adults aged ≥60 years have been included in a Phase 1 and a Phase 2a study of the RSV vaccine clinical development program. In total, 228 individuals aged ≥60 years received an Ad26.RSV.preF based regimen in these studies. Overall, no safety concerns have been raised to date in this population. However, data are very limited, and only brief conclusions have been given for adults ≥60 years. In next Advac reports, the applicant should provide more detailed data by age group (less than 65, between 65-74, 75-84 and 85 and above) and to discuss them (see list of recommendations).

In the Ad26 platform safety data, 1,631 pregnancy cases were reported (majority reported in Ebola vaccine trials in DRC and Rwanda) and 939 final pregnancy outcomes were reported: healthy baby for 781, various other outcomes for 158 pregnancies (including 102 spontaneous abortions), ongoing for 243, and unknown/not reported for 449. Of these 1,631 pregnancies, caesarean section delivery was reported as delivery method in 193 pregnancies and 61 reported normal delivery. Overall, pregnancy outcomes are consistent with what could be expected in sub-Saharan Africa.

For most pregnancies, vaccine exposure took place within 3 months preceding conception (N=464). The number of pregnancy cases is similar for exposure during the first (N=280), second (N=242) or third trimester (N=267) of pregnancy. For 378 cases, time of vaccine exposure was not reported. The number of pregnancies exposed in the first trimester (280) is lower than the threshold of at least 300 pregnancies exposed to reach a conclusion on the effect on malformation ("Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" EMEA/CHMP/203927/2005).

Moreover, although, overall, the cumulative review of pregnancies is promising, a comparison with the frequency of outcomes in pregnancies that were not exposed to Zabdeno is missing to interpret the data adequately.

The majority of the reported solicited AE were of low or mild intensity and lasted for few days after administration of the vaccine. No significant safety issues have been identified to date.

Overall, the Janssen Ad26-based vaccines have an acceptable safety profile in all populations studied, including young adults, children and adolescents, ≥60-year-old, HIV-infected individuals, pregnant women and individuals with pre-existing Ad26 neutralising antibodies. The numbers of children and adolescents, and individuals ≥60-year-old in the safety database is however limited, as well as the number of HIV-infected individuals.

Safety data of Ad26-based vaccine in (older) adults with comorbidities, which are relevant for the COVID-19 vaccine, are lacking. Moreover, it is noted that only about 10% of all subjects in the AdVac safety database were European, and about one third were White.

The absence of safety concern may be considered reassuring in terms of the safety of the Ad26.COV2.S vaccine and other future Ad26 based vaccines. However, safety and reactogenicity may be driven by both the platform and the insert. It is noted that differences in the frequency of solicited AEs were reported across inserts, although the independent effect of the insert on reactogenicity and safety is currently unclear (given the confounding effect of factors such as dose level used, age, region, and pre-existing immunity to the vector). Overall, it remains unclear to which extend the safety profile of Ad26 vaccines can be extrapolated from one insert to another.

2.6.13. Discussion on clinical safety

2.6.13.1. Exposure

The clinical safety database consists of 54,586 adults ≥18 years who received at least one dose of Ad26.COV2.S or placebo regardless of the dose level or schedule in studies COV3001, COV3009, COV2001, COV1002 and COV1001 up cut-off date (22 January 2021 for COV3001 and 11 January 2021 for the others).

Ad26-based vaccine platform clinical safety data, and clinical safety data from studies COV1001 (Phase 1/2a), COV1002 (phase 1 in Japan), COV2001 (phase 2a) (cut-off date for these 3 studies: 11/01/2021) and the phase III trial COV3009 (cut-off date: 14/01/2021, blinded) are supportive.

The assessment of Ad26.COV2.S safety is mainly based on the interim analysis of the results from Phase 3 study COV3001 (cut-off 22/01/2021), comprising 43,783 participants ≥18 years of age who received either a single dose of Ad26.COV2.S at a dose level of $5x10^{10}$ vp (21,895 adults) or placebo (21,888 adults) (Full Analysis Set – FAS). Reactogenicity (solicited local and systemic events) and unsolicited adverse events were collected in a subset of 6,736 participants who received either vaccine (3,356 adults) or placebo (3,380 adults) (Safety subset).

At the time of the primary analysis, the median follow-up after vaccination was 58 days in both groups. Longer safety follow-up of >2 months is available for 23,903 participants in the FAS: 11,948 participants in the Ad26.COV2.S group (54.6%) and 11,955 in the placebo group (54.6%). However, only 34 participants in the Ad26.COV2.S group (0.2%) and 31 in the placebo group (0.1%) have been followed for close to 4 months. Long-term safety is identified as a missing information in the RMP (uncertainties).

In the FAS and the safety subset, the demographic and baseline characteristics were similar among participants who received Ad26.COV2.S or placebo (age, gender, Region, ethnicity, BMI, serostatus at baseline, presence of comorbidities at baseline…).

In the FAS, with a median age of 52 years of age, there were 21,895 adults ≥18 years of age, including 17,636 adults 18-64 yoa (80.5%) and 4,259 adults ≥65 yoa (19.5%) (with 809 adults ≥75 yoa - 3.7%), including 8,936 adults with comorbidities associated with an increased risk of progression to severe COVID-19 (40.8%) (with 2,271 adults ≥65 yoa with comorbidities – 10.4%), and including 2,151 adults seropositive at baseline (9.8%), who received Ad26.COV2.S at the selected dose level of $5x10^{10}$ vp. 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.

In the safety subset, with a median age of 54, there were 3,356 adults ≥18 years of age, including 2,593 adults 18-64 yoa (77.3%) and 763 adults ≥65 yoa (22.7%) (with 150 adults ≥75 yoa – 4.5%), and including 1,135 adults with comorbidities (33.8%) (with 341 adults ≥65 yoa with comorbidities – 10.2%), and including 154 adults seropositive at baseline (4.6%), who received Ad26.COV2.S at the selected dose level of $5x10^{10}$ vp.

The demographic profile of Ad26.COV2.S was generally similar between the safety subset and the FAS, with the exception of race, country, and serostatus at baseline. In the FAS, participants were mainly from US (44.1%), Brazil (16.6%), South Africa (15%); in addition to Colombia (9.7%), Argentina (6.8%), Peru (4%), Chile (2.6%) and Mexico (1.1%). In the safety subset were included only participants from the US (51.5%), Brazil (38.5%) and South Africa (10.1%), for practical reason (Cf. methodology section). In the safety subset, the proportion of White participants was greater (83.4%)

compared to the FAS (58.7%). The proportion of participants who were SARS-CoV-2 seropositive at baseline was lower (4.6%) compared to the FAS (9.6%).

Nevertheless, the safety subset represents a population with diversity by age, gender, race, health status, comorbidities and SARS-CoV-2 serostatus, which includes those most at risk of severe COVID-19 and is representative of a real-life setting.

As a small number of HIV participants were included in COV3001 safety subset. Use in immunocompromised patients is identified as a missing information in RMP (please see discussion below).

Interaction with another vaccine was not studied (missing information in the RMP).

Of note, the demographic and baseline characteristics were also generally well balanced between the Ad26.COV2.S vaccine groups and the placebo groups in supportive studies (COV1001, COV1002, COV2001). All the participants from Study COV1002 came from Japan.

All the adverse reactions reported in the safety subset of the clinical trial COV3001 have been included in the Summary of Product Characteristics.

2.6.13.2. Adverse events

Solicited AEs, unsolicited AEs, SAEs (including deaths), MAAEs and AESIs were evaluated.

Solicited Adverse Events

Reactogenicity in pivotal study COV3001

In the pivotal study COV3001, reactogenicity was assessed in the safety subset.

During the 7-day post-vaccination period, in Ad26.COV2.S group, all solicited local AEs (vaccination site erythema, vaccination site pain, vaccination site swelling) (50.3%) and solicited systemic AEs (fatigue, headache, myalgia, nausea and pyrexia) (55.2%) were reported more frequently than in control group (19.5% and 35.1% respectively).

Pyrexia (defined as body temperature ≥38.0°C, as recorded by the participants) was reported in 9.0% participants in the Ad26.COV2.S group, compared to 0.6% of participants in the placebo group.

The most frequently reported solicited local AE in Ad26.COV2.S group was vaccination site pain (48.7% in Ad26.COV2.S vs. 16.7% in placebo group). The most frequently reported solicited systemic AEs were headache (39% in Ad26.COV2.S group vs. 23.8% in the placebo group), fatigue (38.3% vs. 21.6%, respectively), and myalgia (33.2% vs. 12.8%).

Solicited adverse events were mainly grade 1 or 2. The frequency of Grade 3 solicited AEs was low overall, but higher in participants in the Ad26.COV2.S group (2.2%) compared to participants in the placebo group (0.7%) (no grade 4). The most frequently reported Grade 3 solicited local AE was vaccination site pain reported in 0.3% of participants in the Ad26.COV2.S group (vs. 0.1% in placebo group), and the most frequently reported Grade 3 solicited systemic AEs were fatigue (1% in Ad26.COV2.S vs. 0.3% in placebo) and myalgia (1% vs. 0.2% , respectively).

All solicited local AEs are considered related to study vaccination by definition. Most solicited systemic AEs after vaccination were considered to be related to study vaccine: 98.16% (1819/1853) of the solicited systemic AEs were considered related to the study vaccine, and 95.2% (1131/1188) to the placebo. Regarding the severity, most Grade 3 solicited systemic AEs were considered as related to Ade26.COV2.s, there was only one report of grade 3 headache that was not considered related to the study vaccine.

Most solicited AEs were transient in nature and reported as resolved. Overall, the median duration of the selected solicited AEs was similar in both groups (1 to 2 days after vaccination), and also the median time to onset (within 1 to 3 days after vaccination).

Reactogenicity in supportive studies (COV1001, COV1002 and COV2001)

Overall, the solicited and unsolicited AEs in the supportive studies were consistent with the pivotal phase 3 COV3001 study.

Safety data of a 2-dose regimen of Ad26.COV2.S ($5x10^{10}$ vp) administered at a 56-day interval was available from COV1001 in 77 adults ≥18 to ≤55 years (Cohort 1a) and 81 adults ≥65 years (Cohort 3) of age. In general, no safety concerns were identified after vaccination with two doses of Ad26.COV2.S compare to 1 dose with similar reactogenicity and unsolicited events. By dose, slightly higher frequencies of solicited systemic AEs (main difference regarding pyrexia), and unsolicited AEs were observed post-dose 1 compared to post-dose 2. . Lower frequencies of Grade 3 solicited and unsolicited AEs were observed after a second vaccination with Ad26.COV2.S compared to the first dose in both age groups (adults aged ≥18 to ≤55 and aged ≥65).

Unsolicited Adverse events (COV3001)

As defined in the protocol, for the participants in the safety subset, the investigator was to record systematically all unsolicited AEs, whether serious or non-serious from the time of vaccination until 28 days post-vaccination. Without such a requirement for a systematic collection of all unsolicited events for those participants in the FAS who were not in the safety subset (although spontaneous unsolicited reports were captured in the eCRF), and although a much larger number of subjects have been vaccinated with Ad26.COV2.S in FAS (21,895), the frequencies calculated in the safety subset (3,356 subjects vaccinated with Ad26.COV2.S) is preferred (higher than in the FAS). The selection of unsolicited AEs to be presented in the ADR table in the SmPC was made applying the following criteria (all criteria had to be met): Event occurred with a frequency of at least 0.1% in the safety subset; The AE was not collected as a solicited AE (to avoid duplication of the event in both solicited and unsolicited sections); The unsolicited AE occurred at a higher frequency (of >0.1%) in the Ad26.COV2.S group compared to the placebo group; A medical review was done to establish plausible casual relationship to the vaccine and to assess confounding factors. Moreover, it has been checked that the unsolicited AEs reported in Ad26.COV2.S FAS (applying the same criteria as for the safety subset) are also present in the ADR table.

In the safety subset, the frequency of unsolicited AEs reported during the 28-days post-vaccination period was similar for participants in the Ad26.COV2.S group (13.1%) compared to participants in the placebo group (12%). In the Ad26.COV2.S group, the most frequently reported unsolicited AEs by PT (≥1.0% of participants) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. In the Ad26.COV2.S group, the unsolicited ADRs (not recorded as solicited AEs) selected for the ADR table in the SmPC are chills, arthralgia, malaise, asthenia, muscular weakness and pain in extremity. Most reported unsolicited AEs were Grade 1 or Grade 2 in severity. There was as similar frequency of participants with unsolicited AEs of at least Grade 3 in both group (0.6% in the Ad26.COV2.S group vs. 0.5% in the placebo group). The frequency of unsolicited AEs that were considered related to vaccination was higher in participants in the Ad26.COV2.S group (7.2%) compared to participants in the placebo group (4.6%). There were an imbalance between vaccine and placebo in related unsolicited AEs (difference ≥ 2 related events in favour of vaccine group) observed for cough (12 related with vaccine vs. 4 in placebo), sneezing (10 vs. 8), oropharyngeal pain (5 vs. 1), tremor (3 vs. 1), back pain (3 vs. 1) and hyperhidrosis (2 vs. 0). These related events have been appropriately added in the ADR table in the SmPC.

Five subjects (0.1%) reported 6 unsolicited AEs of at least Grade 3 considered to be related to the study vaccine in the Ad26.COV2.S group (compared to 1 in placebo group): 1 chill, 1 fatigue, 1 malaise, 1 diarrhoea, 1 pain in extremity and 1 headache (none of grade 4).

Of note, no imbalance was observed in the frequency of unsolicited AEs in the Nervous System Disorder class between the Ad26.COV2.S and the placebo group in the FAS or the safety subset (all AEs or related AEs).

Immediate unsolicited reactions occurring within 30 minutes of vaccination were infrequent and occurred in 0.2% of participants in both the vaccine and placebo groups. There were no reports of anaphylaxis immediately following vaccination (at the cut-off).

2.6.13.3. Treatment-emergent AESIs (COV3001)

As, per protocol, there were no pre-specified AESIs for Ad26.COV2.S clinical development, the applicant followed a dynamic medical review of incoming AEs to identify potential safety issues for conditions including, but not limited to immune mediated and/or (neuro) inflammatory events (e.g., hypersensitivity reactions and anaphylaxis, Guillain-Barré Syndrome, Bell's palsy) and thrombotic and thromboembolic events (e.g., pulmonary embolism, deep vein thrombosis). Treatment emergent AESIs were evaluated in the FAS. Up to the cut-off date, in the FAS, the same frequency of subjects reported at least one treatment emergent AESI in both groups (0.6%). Few reported AESIs were assessed as related: 0.2% in the Ad26.COV2.S group compared to 0.1% participants in the placebo group.

Allergic reactions

In this study, the most frequently reported AEs in the broad SMQ 'non-anaphylactic allergic reactions'(≥6 participants in the Ad26.COV2.S group) were rash (24 participants active vaccine including 10 assessed as relate, 16 placebo including 6 related), urticaria (8 participants active vaccine including 3 related, 3 placebo – none related), and hypersensitivity (6 participants active vaccine including 1 related, 4 placebo – none related). Events of urticaria and rash were considered as likely related to the vaccine. Further assessment of the events under the PT 'hypersensitivity' showed most of these events to be either seasonal allergies or allergy to a medication other than the vaccine.

In addition, an SAE of type IV hypersensitivity (Grade 3), not classified as anaphylaxis, was reported in 1 vaccinated individual with rash and erythema from day 2 after vaccination, and urticaria and angioedema of the lips without respiratory distress from day 4. This case does not meet the Brighton Collaboration criteria for anaphylaxis. The event was assessed as Type IV hypersensitivity and was considered likely related to the vaccine due to the close temporal association.

Moreover, since the data lock, the applicant received a SUSAR report of pyrexia, swollen tongue, and dyspnoea from study VAC31518COV3012 (ongoing study in South Africa). The participant received Ad26.COV2.S in an open label fashion. This case with 1 major respiratory criterion (tongue swelling) and 2 minor criterion (dyspnoea and urticaria) meets the Brighton Collaboration case definition criteria for anaphylaxis with level 2 of diagnostic certainty.

Of note, another SUSAR of anaphylaxis was received from the same study, but the event is confounded in underlying COVID-19 infection (the symptoms included headache, fever, chills and dizziness). This case with 1 major cardiovascular criteria of hypotension and no other major or minor criteria does not meet the BCCD of anaphylaxis. Additional information has been requested by the applicant for further assessment.

Hypersensitivity, rash, urticaria and anaphylaxis have been identified as ADRs in the SmPC. Finally, anaphylaxis is considered as an important identified risk in the RMP**.**

Immune-mediated neurological disorders

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

There were 3 cases of Bell's palsy (facial paralysis) in the Ad26.COV2.S group (2 SAE considered as possibly related SAEs by the investigator, but not related by the Sponsor; and 1 non-related AE) compared with 2 cases in the placebo group (non-related). Relatedness to the vaccine cannot be excluded and 2 events of facial paralysis are considered at least possibly related to vaccination. Participants had underlying medical conditions (diabetes, hypertension, obesity) that could also have contributed to the event. Overall, based on the reported data f, a causal relationship between Ad26.COV2.S vaccination and Bell's palsy could not be confirmed nor ruled out. Bell's palsy is included in the list of AESIs taken in consideration for routine and additional pharmacovigilance activities.

Other Nervous system disorders

A numerical imbalance observed between the Ad26.COV2.S group and placebo group for:

- Tinnitus: Six cases of tinnitus were reported in the Ad26.COV2.S group and none in the placebo group. All these cases were considered non-serious. Two cases were considered related by the investigator. Review of the cases revealed no pattern in terms of temporal association with the vaccine (Time to onset range 1 to 22 days). All participants had underlying medical conditions (such as history of tinnitus and migraine, history of hypertension, seasonal allergies and hypothyroidism) or used medications that offered a more plausible alternative cause for the event than the vaccine. None of these events have reported further complications such as hearing loss. In addition, there was only one case of tinnitus in the safety database from the AdVac platform (RSV program).

- Convulsions/seizures: Four cases were reported in the Ad26.COV2.S group (1 serious) and one case (non-serious) in the placebo group, all of which were considered not related to the study vaccine by the investigator. Majority of the subjects had underlying medical conditions (such as dementia/epilepsy and diabetes) were present that could have contributed to the events of convulsions/seizures. The risk of generalised convulsion is included in the list of AESIs taken in consideration for routine and additional pharmacovigilance activities.

Injection site bruising

There were 22 subjects with haemorrhagic disorders in the Ad26.COV2.S group compared to 25 in the placebo group. There were 13 AESIs of injection site bruising (including contusion, haematoma and ecchymosis) with Ad26 5e10 compared to 10 in placebo. An appropriate warning has been specified in SmPC section 4.4 (i.e. 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).

Thromboembolic disorders

A numerical imbalance was observed for the venous thromboembolic events with 11 subjects in the vaccine group vs. 4 in the placebo group. The majority of the participants had underlying medical conditions (such as obesity, hypothyroidism, diabetes) that could have contributed to these events.

In order to assess the impact of vaccination on coagulation, and the risk of inducing a hypercoagulable state, it has been requested to include laboratory tests for the assessment of potential vaccine-induced antiphospholipid syndrome and vaccine-induced activation of coagulation (lupus anticoagulants, anti-beta 2 glycoprotein, anti-cardiolipin and D-dimers), pre and post vaccination in further subjects

enrolled; and to perform assessments of, at least, anti-cardiolipin lgG and lgM, and anti-β2-Glycoprotein 1 IgA, IgG, IgM in frozen serum material pre- and post-first and second vaccination.

One SAE of DVT was reported with Ad26 vaccine (in adult FAS after 28 days after vaccination) in AdVac report V5.

Venous thromboembolism has been included as an important potential risk in the list of safety concerns of the RMP.

Respiratory disorders

AE of asthma was reported for 7 participants in the Ad26.COV2.S group versus 1 participant in the placebo group. For the majority of the participants (including the participant in the placebo group), the assessment of "not related" was made considering the nature of the condition and the subject's medical history (including longstanding history of asthma).

In the Respiratory, thoracic and mediastinal disorders, 10 subjects reported 10 SAEs in the Ade26.COV2.S group (3 Pulmonary embolism, 2 Dyspnoea, 2 Hypoxia, 1 Chronic obstructive pulmonary disease, 1 Pleural effusion, 1 Pneumothorax spontaneous) compared to 4 subjects reporting 6 SAEs in the placebo group (Pulmonary embolism, Dyspnoea, Cough, Oropharyngeal pain, Respiratory distress, Respiratory failure).

Increased HIV acquisition risk

The risk for increased HIV acquisition after vaccination with Ad26-based vaccines is considered to be theoretical. In the AdVac Safety Database V5.0, there were 3 cases of incident HIV infection in Ad26-vaccinated individuals in HIV-V-A004, all captured as SAEs from the same site, which is situated in a high endemic region for HIV infection (all cases presenting risk factors for HIV infection) (compared to none in the placebo group). In study VAC52150EBL2002 (Ebola vaccine), one adult male participant tested HIV seropositive approximately 1 year after receipt of one dose of Ad26.ZEBOV (sexually inactive at study enrolment; no further information available about risk factors for HIV infection). There have been no HIV infections reported in the development programs of RSV, Filovirus, and malaria Ad26-vectored vaccines. To date, there were no incident HIV infections reported in clinical studies with Ad26.COV2.S. The next version of the The applicant is recommended to submit the Adenoviral Vaccine Safety Database (V6.0) including a discussion of the potential increased risk of HIV acquisition in individuals vaccinated with adenovirus-based vaccines with a review of reported cases in the updated Ad26 platform data (expected for approximatively April 2021) (see list of recommendations).

Conclusion on AESIs

Besides the numerical imbalances described above, there were no notable patterns or numerical imbalances between the Ad26.COV2.S and placebo group for treatment-emergent AESIs (including neurologic, neuroinflammatory, and cardiovascular events) that would suggest a causal relationship to the Ad26.COV2.S vaccine. The overall total number of cases of AEs of interest observed in the study were low and within the rates observed in the general population. For the majority of the reported AESIs, because of lack of plausible biological mechanism, not plausible time to onset, alternative explications (such as underlying pathologies) and confounding factors, a causality could not be clearly established. Finally, the absence of a clear causal association is further enforced by the safety data from the platform.

SAEs and deaths

Pivotal study COV3001

In study COV3001, SAEs (including deaths) were evaluated in the FAS.

Fewer deaths were observed in the Ad26.COV2.S group (3, none confirmed to be associated with COVID-19) compared to the placebo group (16, including 6 confirmed to be associated with COVID-19). All 3 deaths reported in the Ad26.COV2.S group were assessed by the investigator as not-related to vaccination: fatal SAE of lung abscess , fatal SAE of pneumonia , and 1 death of unknown cause at the time of data cut-off .

Until the cut-off date, in the FAS, 90 (0.4%) subjects in the Ad26.COV2.S group and 137 (0.6%) subjects in the placebo group reported 1 or more non-fatal SAEs. However, a total of 83 (0.4%) subjects reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared to 96 (0.4%) subjects in the placebo group. SAEs associated with COVID-19 were reported in the infections and infestations and in the investigations (preferred term: SARS-CoV_2 test positive) SOCs.

Among the SAEs not associated with COVID-19, overall, no major imbalances were observed by SOC. The most frequently reported SAEs by SOC in the Ad26.COV2.S and placebo groups were infections and infestations and nervous system disorders.

For the nervous system disorders, 10 subjects reported 12 SAEs in the COVID-19 group (compared to 8 subjects reporting 8 SAEs in the placebo group). Six SAEs are considered related to the Ad26.COV2.S (2 Facial paralysis, 1 Cerebral haemorrhage, 1 Guillain-Barre syndrome, 1 Radiculitis brachial and 1 Transverse sinus thrombosis: please Cf. AESIs discussed before). None were considered related in the placebo group.

For the respiratory, thoracic and mediastinal disorders, an imbalance was observed with 10 subjects reported 10 SAEs in the COVID-19 group (3 Pulmonary embolism, 2 Dyspnoea, 2 Hypoxia, 1 Chronic obstructive pulmonary disease, 1 Pleural effusion, 1 Pneumothorax spontaneous) compared to 4 subjects reporting 6 SAEs in the placebo group (Pulmonary embolism, Dyspnoea, Cough, Oropharyngeal pain, Respiratory distress, Respiratory failure). None were assessed as related to vaccine in both groups.

An imbalance was also observed for the hepatobiliary disorders with 4 subjects reported 4 SAEs in the COVID-19 group (2 Cholecystitis acute, 1 Cholecystitis, 1 Cholelithiasis) compared to 1 subject reporting 1 SAE in the placebo group (Cholecystitis chronic). None were assessed as related to vaccine in both groups.

There were no (S)AEs leading to discontinuation.

Supportive studies (COV1001, COV1002 and COV2001)

Safety data on deaths, SAEs, and AEs leading to study discontinuation are available from supportive clinical studies COV1001, COV1002, COV2001, and COV3009. The studies include >10,500 participants ≥18 years of age who received either placebo or active vaccine at doses up to $1x10^{11}$ vp (the vast majority had only a follow up of 26 days). As of the cut-off date, only 1 death was reported (accidental death of a COV3009 participant). Few SAEs and early discontinuations due to AEs were observed in all groups. The available data from the supportive studies does not raise any safety concern.

Medically attended Adverse Events

Pivotal study COV3001

In study COV3001 MAAEs were evaluated in the FAS

Until the cut-off date, in the FAS, 1.4% participants reported one or more MAAEs in the Ad26.COV2.S group compared to 1.9% participants in the placebo group. Overall, no major imbalances were observed by SOC. The most frequently reported MAAEs by SOC in the COVID-19 vaccine and placebo

groups were infections and infestations (0.5% in the Ad26.COV2.S group and 0.8% in the placebo group). By PT, COVID-19 infection was the most frequently reported MAAE for 16 (0.1%) of participants in the Ad26.COV2.S group compared to 35 (0.2%) participants in the placebo group.

When evaluating the MAAEs not associated with Covid-19, up to the cut-off date, 286 (1.3%) participants reported one or more MAAEs in the Ad26.COV2.S group compared to 361 (1.6%) participants in the placebo group (and 0.3% grade 3 in each group). As expected, the majority of MAAEs associated with COVID were in the infections and infestation SOC.

There were 0.1% of related MAAEs (not associated with covid-19) in both groups. Most of these are discussed in the SAE and AESI sections. In the Ad26.COV2.S group, the MAAEs were mainly in the following SOCs: nervous system (2 facial paralysis, 2 headache, 1 Guillain-Barre syndrome, 1 radiculitis brachial, 1 syncope) and general disorders and administration site conditions (2 pyrexia, 1 chills, 1 influenza like illness, 1 injection site reaction, 1 vaccination site hypersensibility, 1 vaccination site swelling).

2.6.13.4. Clinical laboratory parameters

An evaluation of the clinical laboratory parameters was included in COV1001, COV1002a and COV2001 (haematology, chemistry and urinalysis in COV1001, haematology and chemistry in COV1002a, and haematology in COV2001). Overall, a low number of laboratory abnormalities were reported as an AE after vaccination with Ad26.COV2.S.

2.6.13.5. Safety by subgroup (COV3001)

Overall, the safety profile of Ad26 5x1010 was similar independently of the subgroups, in particular the frequencies of subjects with SAEs, MAAEs and AESIs (rare). In the Ad26 5x1010 group, for all subgroups, most solicited AEs were Grade 1 or Grade 2 in severity, and most solicited AEs were transient in nature and reported as resolved. The nature of the local and systemic AEs recorded was similar, showing the same pattern as for the pooled population. However, the following differences were noted:

By age group: The reactogenicity was milder and lower in older adults aged ≥65 years compared to the younger adults aged ≥18 to 64. Overall, the demographic and baseline characteristics were consistent between the different age subgroups. However, as expected, in the Ad26 5x1010 group (safety subset), there were less comorbidities at baseline in the younger group (31% for subjects 18 to 64 years of age), compared to the older group (45% for subjects ≥65 years of age).

Adults with comorbidities at baseline: The reactogenicity was lower in participants with any comorbidity at baseline than in adults without any comorbidity. The difference in reactogenicity profile by comorbidities was observed in adults aged 18-64, but no difference was observed in adults aged ≥65.

Subjects 18-64 years of age with comorbidities at baseline reported less local solicited AEs than the subjects 18-64 years of age without comorbidities, and less systemic solicited AEs than the subjects 18-64 yoa without comorbidities.

Subjects from 65 years of age with comorbidities at baseline reported similar reactogenicity than the subjects from 65 years of age without comorbidities.

By Region: Subjects from Northern America reported a higher percentage of reactogenicity than subjects from Latin America and Southern Africa. However, differences in the demographic and

baseline characteristics, as well as cultural differences in AE reporting in clinical practice, could interfere with this observation.

By gender: Females reported a higher percentage of reactogenicity than males (although both subgroups had a similar median age).

By baseline seropositivity: The nature of the local and systemic AEs recorded was similar, showing the same pattern as for the pooled population, without any clinically meaningful differences in frequencies. However, the number of vaccinated subjects who were seropositive at baseline is too limited in the safety subset to draw any definitive conclusions.

Seronegative subjects 18-64 years of age reported similar frequency of local solicited AEs than the seropositive subjects 18-64 years of age, and slightly more systemic solicited AEs than the seropositive subjects 18-64 years of age.

Seronegative subjects from 65 years of age reported less local solicited AEs than the seropositive subjects from 65 years of age, and similar frequency of systemic solicited AEs than the seropositive subjects from 65 years of age.

By HIV infection at baseline: The frequency of local and systemic solicited AEs was slightly lower in HIV infected adults at baseline. However, the number of vaccinated subjects HIV infected at baseline is too limited in the safety subset to draw any conclusions regarding reactogenicity (34 in Ad26.COV2.S group and 25 in placebo group).

Concomitant therapies

The frequencies of subjects with local and systemic solicited AEs were clearly lower in subjects who did not use antipyretics / analgesics (A/A) post-vaccination compared to those who used A/A in the Ad26.COV2.S group (and also for the grade 3 solicited AEs). The frequencies of subjects with solicited AEs were slightly lower in subjects who did not use corticosteroids compared to those who used corticosteroids in the Ad26.COV2.S group.

Use in pregnancy

In COV3001, up to the cut-off date of 31 December 2020, 8 pregnancies were reported in the GMS database for this study: 4 in COVID-19 vaccine group and 4 in placebo group. In the COVID-19 group, 2 pregnancies were still ongoing, and there were 1 spontaneous abortion and 1 ectopic pregnancy (both assessed as not related to vaccine). In the placebo group, 1 pregnancy was still ongoing, and there were 1 incomplete abortion and 2 elective abortions.

In the Ad26 platform safety data (cut-off 21 December 2020), of the 1,631 unique pregnancies (majority reported in Ebola vaccine trials in DRC and Rwanda), 939 final pregnancy outcomes were reported: healthy baby for 781, various other outcomes for 158 pregnancies (including 102 spontaneous abortions), ongoing for 243, and unknown/not reported for 449. Overall, pregnancy outcomes are consistent with what could be expected in sub-Saharan Africa.

The number of pregnancy cases reported is similar for exposure during the first (N=280), second (N=242) or third trimester (N=267) of pregnancy. For 378 cases, time of vaccine exposure was not reported. The number of pregnancies exposed in the first trimester (280) is lower than the threshold of at least 300 pregnancies exposed to reach a conclusion on the effect on malformation ("Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" EMEA/CHMP/203927/2005).

Although, overall, the cumulative review of pregnancies did not reveal any safety concern related to Ad26-based vaccine exposure during pregnancy, a comparison with the frequency of outcomes in

pregnancies that were not exposed to the Ad26 -vaccine is missing in order to interpret the data adequately.

The applicant has categorised the use of Ad26.COV2 during pregnancy as an area of missing information in the RMP. An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants (Trial VAC31518COV2004) and a COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) are planned.

In COV3001, up to the cut-off date of 31 December 2020, 285 breastfeeding women (128 in Ad26.COV2.S group and 157 in placebo group) were enrolled. However no further information regarding breastfeeding was requested during the study. Use in pregnancy and while breastfeeding is considered as missing information in the RMP.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study VAC31518COV3001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA, to confirm the safety profile of Ad26.COV2.S COVID-19 vaccine and provide long term safety data.

2.6.14. Conclusions on the clinical safety

The safety evaluation of Ad26.COV2.S vaccine is based on the interim analysis of the results from Phase 3 study COV3001 (cut-off 22/01/2021), comprising 43,783 participants ≥18 years of age who received either a single dose of Ad26.COV2.S at a dose level of $5x10^{10}$ vp (21,895 adults) or placebo (21,888 adults) with a median of 2 months of follow-up after vaccination. Reactogenicity was collected in a subset of 6,736 participants who received either vaccine (3,356 adults) or placebo (3,380 adults).

The safety of Ad26.COV2.S is mainly characterised by local and systemic reactions occurring during the first 7 days after vaccination. Reactions were mostly mild to moderate and transient. The reactogenicity was milder and lower in older adults aged ≥65 years compared to the younger adults aged ≥18 to 64. There has been observed higher reactogenicity in females than in males and lower reactogenicity in subjects with 1 or more baseline comorbidities than those without any comorbidity, mainly observed in participants aged 18-64. There was no major difference in the reactogenicity between seropositive and seronegative participants at baseline and by race/ethnicities.

SAEs and AESIs were infrequent in the Ad26.COV2.S and placebo groups. Although no specific risk has been identified, a causal relationship between Ad26.COV2.S vaccination and Guillain-Barré Syndrome, Bell's Palsy and chronic pulmonary disorders exacerbation (i.e. asthma and COPD) could not be confirmed nor ruled out. Guillain-Barré Syndrome and Bell's Palsy are included in the list of AESI and taken in consideration for routine and additional pharmacovigilance activities. The risk of exacerbation of chronic pulmonary disorders (i.e. asthma and COPD) might be further monitored in the planned PASS if feasibility is confirmed.

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), and Venous thromboembolism are considered as important potential risks. Anaphylaxis is considered as an important identified risk. More frequently reported AESIs in the vaccine group, rash, urticaria, and hypersensitivity are included as Adverse reactions in the PI. Anaphylaxis has also been included in the SmPC section 4.8.

In conclusion, the observed safety profile is considered as favourable.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA: the MAH should submit the final clinical study report for the randomised,

placebo-controlled, observer-blind study VAC31518COV3001. The study subjects are expected to be followed for 24 months after the first dose. (see Annex II of the product information).

Regarding missing data to confirm safety in subpopulations that were not studied or whose data are limited please refer to section 2.7.

2.7. Risk Management Plan

Safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Sunmmary of safety concerns

Important identified risks	• Anaphylaxis
Important potential risks	• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Venous thromboembolism
Missing information	• Use in pregnancy and while breastfeeding • Use in immunocompromised patients • Use in patients with autoimmune or inflammatory disorders • Use in frail patients with comorbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Interaction with other vaccines • Long-term safety

Risks considered important for the inclusion in the summary of safety concerns

Anaphylaxis has been added as an important identified risk based on one confirmed case of anaphylaxis (Brighton Collaboration Level 2 of diagnostic certainty) reported in the open label study VAC31518COV3012.

Anaphylaxis is known to possibly occur with any injectable vaccine. Ad26.COV2.S contains polysorbate 80 whose structure presents similarities with PEG, recently suspected to be involved in anaphylactic reactions with mRNA vaccines. The potential for polysorbate 80 to trigger hypersensitivity and the possibility of cross-reactivity between PEG and PS80 have been discussed in the literature[3;4]. Cases of PS80-induced hypersensitivity have been reported and have involved different drugs, including a vaccine, and different routes of administration, including intramuscular [5;6;7].

Anaphylaxis is also anticipated to be reported in the context of large-scale vaccination, where many more individuals will be vaccinated. Moreover, mass vaccination campaigns may involve healthcare

[3] Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med. 2020 Dec 30:NEJMra2035343.
[4] Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, Hemler JA, Phillips EJ. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. J Allergy Clin Immunol Pract. 2019 May-Jun;7(5):1533-1540.e8.
[5] Palacios Castaño MI, Venturini Díaz M, Lobera Labairu T, González Mahave I, Del Pozo Gil MD, Blasco Sarramián A. Anaphylaxis Due to the Excipient Polysorbate 80. J Investig Allergol Clin Immunol. 2016;26(6):394-396.
[6] Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, Hemler JA, Phillips EJ. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. J Allergy Clin Immunol Pract. 2019 May-Jun;7(5):1533-1540.e8.
[7] Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. BMJ Case Rep. 2012 May 8;2012:bcr0220125797.

professionals who do not routinely administer vaccines and should therefore be fully aware of the risk minimisation measures related to anaphylaxis. Anaphylaxis is thus considered as an important identified risk.

The analysis of safety data provided in the cMAA identified *Venous thromboembolism* as an important potential risk: inclusion was proposed, based on the numerical imbalance observed in the Ad26.COV2.S group vs the placebo group (i.e. 11 vs 4 cases; including 6 vs 2 SAEs) (refer to section 2.6.5 for further details). Additional PV activity are planned to further characterise this risk. It is recommended that the study will include laboratory testing for evaluating potential vaccine-induced antiphospholipid syndrome and vaccine-induced activation of coagulation by measuring lupus anticoagulants, anti-beta 2 glycoprotein, anti-cardiolipin and D-dimers.

'*Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)*' was included as an important potential risk. At this stage, VAERD/VAED is still a theoretical risk. Non-clinical studies with Ad26.COV2.S-immunised Syrian hamsters and NHP did not show evidence of VAED or VAERD, but showed an induction of neutralising antibodies and a Th1-skewed immune response after Ad26.COV2.S dosing, suggesting that the theoretical risk of VAERD and VAED for Ad26.COV2.S is low. Data from clinical trials did not show any indication of the presence of VAED, including VAERD. However, as long-term safety and efficacy data are not yet available, the risk VAED/VAED remains an important potential risk.

Missing information:

'*Use in pregnancy and while breastfeeding*': considering the limited data in pregnant women vaccinated with the Ad26.COV2.S vaccine (i.e. 8 pregnancies reported for trial COV3001; 4 in Ad26.COV2.S group and 4 in placebo group) and the planned Phase 2 study VAC31518COV2004, this issue should be included as missing information and further characterised as part of the pharmacovigilance plan.

Considering the limited data in vaccinated breastfeeding women (i.e. 128 breastfeeding women received Ad26.COV2.S in trial COV3001), this population is considered as missing information.

'Use in immunocompromised patients': the Ad26 platform data in HIV infected adults and the absence of replication of Ad26.COV2.S suggest that no safety issue is expected in this population. This should be further supported by clinical data from trial COV3009 as available. At the time of cMAA, no safety issue was raised in HIV subjects vaccinated with Ad26.COV2.S in the trial COV3001. However, only a very limited number of vaccinees were included in the Full Analysis Set (i.e. 601 (2.7%)). Moreover, HIV patients under treatment may represent a distinct population from other immunocompromised subjects, including patients under immunosuppressive treatment, transplant patients or patients with hereditary and/or acquired immunodeficiency disease states. Additional pharmacovigilance activities are planned to monitor this safety concern.

'Use in patients with autoimmune or inflammatory disorders': other sub-populations with clinical conditions stable under non-immunomodulator treatment (e.g. autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) were included at very low number clinical development precluding the provision of meaningful data. This safety concern will be monitored as part of the pharmacovigilance plan.

'Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)': subjects with comorbidities associated with increased risk of severe COVID-19 were included in the clinical development plan: i.e. 8,936 (40.8%) of vaccinees with one or more comorbidities were included in the COV3001 Full Analysis Set. However, the safety and efficacy of frail subjects who also have comorbidities associated with increased risk for severe COVID-19 has not yet been assessed and is considered as missing information. Additional pharmacovigilance activities are planned to characterise this missing information.

'Interaction with other vaccines': co-administration of Ad26.COV2.S with other vaccines has not been evaluated in clinical trials. However, data on interaction, mainly with flu and pneumococcal vaccines which are often given to elderly, are needed for vaccinators and prescribers. An interventional clinical trial is planned to further characterise this missing information.

'Long term safety data': long term safety data are available at the time of the cMAA. The relevance of the long-term follow-up is discussed, and adequate pharmacovigilance activities are proposed.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications. As usually observed, the reactogenicity profile differs with age, with lower and milder reported solicited events in older adults.

Anxiety-related reactions can occur in anticipation or as a result of an injection of any kind. These reactions are not related to the vaccine, but to fear of the injection. The most commonly reported manifestations are fainting (syncope and presyncope), hyperventilation, vomiting. A statement on those reactions is included in section 4.4, and it is agreed that they do not require further characterisation or risk minimisation.

Vaccination errors may be introduced in the context of mass vaccination campaign. The following situations have been identified as potential source of immunisation errors: risk to erroneously administer Ad26.COV2.S twice as a 2-dose schedule is implemented for other authorised vaccines in EU; risk to administer a higher dose of Ad26.COV2.S as multidose vials will be used, risk for Ad26.COV2.S being erroneously administered in adolescents aged 16-17 years as this age group is included in the indication of other manufacturer's COVID-19 vaccines, and finally risk of mixed schedule. . Risk minimisation activities in the form of communication messages in the PI are considered adequate to minimise the risk. Vaccination errors reports will be monitored in the PSURs and monthly reports.

'Exacerbation of chronic pulmonary disorders (i.e. asthma and COPD)': (i.e. asthma and COPD)' An AE of asthma was reported for 7 participants in the Ad26.COV2.S group versus 1 participant in the placebo group. For the majority of the participants (including the participant in the placebo group), the assessment of "not related" was made considering the nature of the condition and the subject's medical history (including longstanding history of asthma). Besides, 1 subject reported 1 SAE of Chronic obstructive pulmonary disease in the COVID-19 group compared to none in the placebo group. Although the causality is not clear, because there is an imbalance with a significative number of cases with Ad26.COV2.S, the risk of exacerbation of chronic pulmonary disorders (i.e. asthma and COPD) should be followed.

Adverse events of special interest (AESI) are taken in consideration for routine and additional pharmacovigilance activities.

A set of AESI has been identified taking into consideration the available lists of AESIs from the Brighton Collaboration (SPEAC) (Law 2020), ACCESS protocol (2020), US CDC (preliminary list of AESI for VAERS surveillance) (Shimabukuro 2020), and MHRA (unpublished guideline).

The proposed list of AESI is considered dynamic and may change following the evolving safety profile of the vaccine. Currently, medical conditions covered by the list of AESIs include Immune-mediated and (neuro-)inflammatory disorders (including Guillain-Barré syndrome and Bell's palsy), Thrombotic and thromboembolic events, Major organ disorders (including neurological, cardiovascular, hepatic, and respiratory), Events associated with COVID-19.

Conclusions on the safety specification

It is agreed that the list of safety concerns in the RMP are appropriate.

Pharmacovigilance plan

Routine pharmacovigilance activities

The applicant will follow standard pharmacovigilance processes, along with the additional actions referenced in the EU-RMP. The applicant has a Global Safety Database in place to manage the receipt, processing, and reporting of individual and aggregate safety data to regulatory authorities, and to support pharmacovigilance activities including safety signal detection and ongoing evaluation of the benefit-risk profile of the vaccine.

ICSR reporting

The applicant will submit Individual Case Safety Reports (ICSRs) in accordance to EMA GVP guidance.

Follow-up for spontaneous and solicited ICSRs

ICSRs are followed up promptly to obtain additional information relevant to the report as necessary to provide a complete description of the safety event.

Two specific adverse reaction **follow up questionnaires** will be used to collect follow-up information on reports of anaphylaxis, and vaccination failure/lack of effect, including events of VAED and VAERD.

Monthly summary safety reports

In line with EMA's 'Consideration on core requirements for RMPs of COVID-19 vaccines' guidance. the applicant will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data. Topics covered by the monthly safety reports will include, at a minimum:

- Interval and cumulative number of reports stratified by report type (medically confirmed/not) and by seriousness (including fatal separately).
- Interval and cumulative number of reports, overall and by age groups, and in special populations (e.g. pregnant women).
- Interval and cumulative number of reports per High Level Term and System Organ Class.
- Summary of the designated medical events.
- Reports per EU country.
- Exposure data (including per EU country).
- Changes to reference safety information in the interval.
- Ongoing and closed signals in the interval.
- AESI and RMP safety concerns reports – numbers and relevant cases, including O/E analysis, where appropriate.
- Fatal reports – numbers and relevant cases, including O/E analysis, where appropriate.
- Risk/benefit considerations.

Pregnancy outcomes and sudden death are AEs of interest that will each be discussed in separate sections of the periodic reports.

The need and frequency of submission of the summary safety reports will be reevaluated based on the available evidence from post-marketing six months after the conditional marketing authorisation of the vaccine.

Literature review

Literature monitoring for Ad26.COV2.S includes both an automated daily search for published and pre-publication/online first references in 2 commercial database products (Embase and Ovid Medline), as well as a daily manual review of one or more literature aggregator services. Search criteria include any COVID-19 vaccine product, irrespective of manufacturer or vaccine technology, and a report of AE(s) without restriction by seriousness or severity. References retrieved by the above search strategies are reviewed by a healthcare professional and are escalated based on reporting of either new safety observations or new aspects of known risks that require further assessment.

Signal Investigation

All available safety information across clinical investigations, post-marketing data, and all other sources of information is reviewed on a regular basis. Other sources of pertinent data may include nonclinical studies, manufacturing and product quality reports, relevant publications, epidemiology data, data from external safety databases, safety-related health authority and healthcare provider queries, and safety-related health authority communications and assessment reports.

Routine aggregate signal detection will include regular surveillance of AE reports received in the applicant's Global Safety Database, irrespective of country of origin, seriousness, medical confirmation, or validity, as well as reviews of external databases. The Table below shows an outline of data sources and frequency of monitoring.

Data source	Frequency of monitoring
applicant's database	Weekly for temporal and disproportionality analyses
	Time to onset analysis as proof of concept every 2 weeks
FDA VAERS	Weekly data review and monthly data mining
EudraVigilance	Weekly data mining
WHO VigiBase	Data mining every 3 months

Methods for signal detection activities will include:

a. Disproportionality analysis

b. Time-to-onset analysis

c. Temporal analysis

d. O/E analysis, when applicable

Traceability

The SmPC includes instructions for healthcare professionals to:

- clearly record the name and lot number of the administered vaccine to improve traceability (SmPC section 4.4);
- report any suspected adverse reactions including batch/lot number if available (section 4.8).

Traceability is available for every shipping container of Ad26.COV2.S, which is fitted with a unique device that provides real-time monitoring of geographic location 24 hours per day, 7 days per week. Each device will also trace the batch/lot of the associated shipment. The device is activated prior to shipment and information is transmitted wirelessly to the applicant at a predefined cadence until delivery to each country's government distribution center. Each shipment will be accompanied by a passive temperature datalogger. Alarms for excursions (per predefined specifications) are programmed into the device. If the display on the device doesn't show an alarmed status, the vaccine can be received. If the display shows an alarmed status, the product needs to be stored in the appropriate temperature conditions upon arrival and the receiver needs to follow the applicant's instructions for reporting an alarmed shipment. These data may be used for the assessment of a safety signal.

The vaccine carton box also includes a 2D matrix barcode which has the batch/lot number, GTIN product code, and expiry date, should there be capability at a vaccination site to utilise this as an information source.

Further, the applicant will make available vaccination cards to vaccinees that may be completed at the time of vaccination. The vaccination cards contain the following elements:

- Pre-printed vaccine brand name and manufacturer name.
- Placeholder space for name of vaccinee.
- Placeholder space for date of vaccination and associated lot number.
- For EEA countries, reference to the National Reporting System for AE reporting.
- QR code and URL (www.covid19vaccinejanssen.com) for additional product information.

In addition to the vaccination cards, 2 stickers per dose, containing pre-printed vaccine brand name, lot information, and a 2D matrix barcode will be made available to support documentation of the lot information on both the vaccination cards for vaccinees and in the vaccinee medical records in mass vaccination centers. It is acknowledged that some countries may require utilisation of nationally mandated vaccination cards or electronic systems to document the lot number; therefore, the available vaccination cards and stickers with printed lot information may not be utilised in all countries. The use will depend on national requirements and/or national competent authority guidance.

The following milestones apply for the availability of the stickers with printed lot information:

- For EEA countries: sticker sheets with printed lot information will be provided at the same time and alongside the vial cartons from initial launch.
- Projected 2022: Upon development and approval of single-dose vials, stickers with printed lot information will be available inside the vial box or carton around it.

The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Additional pharmacovigilance activities

The applicant proposes the **following 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 (five safety and two on effectiveness).

The following Table outlines proposed additional pharmacovigilance activities in RMP version 1.4

Summary of pharmacovigilance and risk minimisation measures

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older (VAC31518COV3001) Ongoing	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.	Anaphylaxis Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety	Final study report	31 December 2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities				
A randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older (VAC31518COV3009) Ongoing	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of 2 doses of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.	Anaphylaxis Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) Long-term safety	Final study report	30 June 2024
An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants (VAC31518COV2004) Planned	To assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adult participants during the 2nd and/or 3rd trimester of pregnancy, to assess the safety and reactogenicity of Ad26.COV2.S (potentially) post-partum, and to assess pregnancy outcomes. To assess the presence of immunoglobulins against SARS-CoV-2 in colostrum and breast milk.	Use in pregnancy and while breastfeeding	Protocol submission Final study report	06 March 2021 30 September 2023
Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients Planned	To assess the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.	Use in immunocompromised patients	Final study report	30 June 2023
COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) (VAC31518COV4005) Planned	To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.	Use in pregnancy and while breastfeeding (*This study will only address use in pregnancy)*	Protocol submission Final study report	15 February 2021 30 June 2027

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Post-authorisation, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe (VAC31518COV4003) Planned	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.	Anaphylaxis Venous thromboembolism Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety Use in pregnancy and while breastfeeding *(The adequacy of the study to address pregnancy outcomes is to be assessed. The safety of Ad26.COV2.S in breastfeeding women will not be studied.)*	Protocol submission Final study report	15 May 2021 30 June 2024
Post-authorisation, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe (VAC31518COV4004) Planned	To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalisations up to 2 years post-vaccination.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in immunocompromised patients	Protocol submission Final study report	31 March 2021 30 June 2024
Post-authorisation, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States (VAC31518COV4001) Planned	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.	Anaphylaxis Venous thromboembolism Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety	Protocol submission Final study report	30 June 2021 31 December 2024
Post-authorisation, observational study to assess the effectiveness of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States (VAC31518COV4002) Planned	To estimate the effectiveness of Ad26.COV2.S in preventing medically-attended COVID-19 up to 2 years post-vaccination.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in immunocompromised patients	Protocol submission Final study report	30 June 2021 31 December 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Coadministration study of Ad26.COV2.S with seasonal influenza vaccine Planned	To assess the safety and immunogenicity of Ad26.COV2.S and seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines	Interim analysis report Final study report	31 December 2022 31 December 2023
A randomized, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive (VAC31518COV2001) Ongoing	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and as a 2-dose or a 1-dose schedule.	Venous thromboembolism	Final study report	31 December 2023

Overall conclusions on the Pharmacovigilance Plan

The proposed additional pharmacovigilance activities are appropriate for further characterisation the safety profile of the product and considering the pandemic circumstances.

Risk minimisation measures

Routine risk minimisation activities only are proposed to manage the safety concerns of the medicinal product. This is acceptable.

Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Anaphylaxis	**Routine risk minimisation measures:** SmPC Section 4.3 PL Section 2 PL Section 4 SmPC Section 4.4 provides recommendations to address the risk of anaphylaxis. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TFUQ for the characterisation of anaphylactic/anaphylactoid reactions **Additional pharmacovigilance activities:** Trial VAC31518COV3001 Final study report: 31 December 2023 Trial VAC31518COV3009 Final study report: 30 June 2024 Study VAC31518COV4003 Final study report: 30 June 2024 Study VAC31518COV4001 Final study report: 31 December 2024

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD **Additional pharmacovigilance activities:** Trial VAC31518COV3001 Final study report: 31 December 2023 Trial VAC31518COV3009 Final study report: 30 June 2024 Study VAC31518COV4004 Final study report: 30 June 2024 Study VAC31518COV4002 Final study report: 31 Dec 2024
Venous thromboembolism	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Trial VAC31518COV3001 Final study report: 31 December 2023 Trial VAC31518COV3009 Final study report: 30 June 2024 Study VAC31518COV4003 Final study report: 30 June 2024 Study VAC31518COV4001 Final study report: not yet available Trial VAC31518COV2001 Final study report: 31 December 2023
Missing Information		
Use in pregnancy and while breastfeeding	**Routine risk minimisation measures:** • SmPC Section 4.6 (only for use in pregnancy) • PL Section 2 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3001 (This trial will only address use while breastfeeding) Final study report: 31 December 2023 • Trial VAC31518COV3009 (This trial will only address use while breastfeeding) Final study report: 30 June 2024 • Trial VAC31518COV2004 Final study report: 30 September 2023 • Study VAC31518COV4005 (This study will only address use in pregnancy) Final study report: 30 June 2027

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in immunocompromised patients	**Routine risk minimisation measures:** SmPC Section 4.4 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients Final study report: 30 June 2023 Study VAC31518COV4003 Final study report: 30 June 2024 Study VAC31518COV4004 Final study report: 30 June 2024 Study VAC31518COV4001 Final study report: 31 Dec 2024 Study VAC31518COV4002 Final study report: 31 Dec 2024
Use in patients with autoimmune or inflammatory disorders	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study VAC31518COV4003 Final study report: 30 June 2024 Study VAC31518COV4001 Final study report: 31 Dec 2024
Use in frail patients with comorbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Trial VAC31518COV3001 Final study report: 31 December 2023 Study VAC31518COV4003 Final study report: 30 June 2024 Study VAC31518COV4001 Final study report: 31 Dec 2024

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Interaction with other vaccines	**Routine risk minimisation measures:** SmPC Section 4.5 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Coadministration study of Ad26.COV2.S with seasonal influenza vaccine Final study report: 31 December 2023
Long-term safety	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Trial VAC31518COV3001 Final study report: 31 December 2023 Trial VAC31518COV3009 Final study report: 30 June 2024 Study VAC31518COV4003 Final study report: 30 June 2024 Study VAC31518COV4001 Final study report: 31 Dec 2024

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 25 February 2021. The new EURD list entry will therefore use the 25 February 2021 to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S) has not been previously authorised in a medicinal product in the European Union.

The active substance Ad26.COV2.S is a recombinant adenoviral vector that contains the sequence that encodes the SARS-CoV-2 spike glycoprotein. After administration, the replication incompetent adenoviral particles will infect cells and the sequence encoding the SARS-CoV-2 spike glycoprotein will be transcribed into mRNA and subsequently translated into SARS-CoV-2 spike glycoprotein (which will

serve as antigen to evoke an immune response). Although the adenoviral particle itself does not contain any SARS-CoV-2 spike glycoprotein, the coding sequence of the SARS-CoV-2 spike glycoprotein is an integral part of the genome of the adenoviral construct. Therefore, the adenoviral particle as an entity should be considered as active substance (and not just the coding sequence of the SARS-CoV-2 spike glycoprotein).

Although recombinant replication incompetent adenovirus serotype 26 has been previously used in different constructs, this vector has never been used for expression of SARS-COV-2 spike glycoprotein and/or as a Covid-19 viral vector vaccine.

Other Covid-19 vaccines or medicinal products that are currently registered do not contain recombinant replication incompetent Ad26 viral vector expressing SARS-CoV-2 spike glycoprotein as active substance.

In conclusion, since a medicinal product containing recombinant, replication-incompetent adenovirus serotype 26 vectored vaccine encoding the SARS-CoV-2 spike glycoprotein has not been previously authorised in the EU, the active substance Ad26.COV2.S (recombinant, replication-incompetent adenovirus serotype 26 vectored vaccine encoding the SARS-CoV-2 spike glycoprotein) is considered a new active substance in itself.

The CHMP, based on the available data, considers adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S) to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

Labelling exemptions

The following exemptions from labelling and serialisation requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.1, from 16 December 2020) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

EU packaging specific derogations

a) Outer and immediate labelling in English only (from start of supply until end 2021)

Outer and immediate labelling will be provided in English only for all EU Member States, as well as Norway and Iceland.

Country/language specific outer/immediate labelling shall be provided in all EU languages by beginning 2022.

This exemption is justified on the necessity to provide maximum flexibility of supply and speed of

vaccine production/deployment due to the ongoing pandemic. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. The use of unified English-only pack components will allow the vaccine to be distributed across multiple countries simultaneously.

A QR code and URL printed on the outer carton, QR card and the patient information leaflet will provide access to the product information in the national language(s).

b) Printed package leaflet in English only (from start of supply until end 2021)

A printed package leaflet (PL) will be provided in the national language(s) for those MSs that require so. All other MSs, that have granted a temporary exemption for an English-only PL, will receive the English printed PL. Moreover, the MAH shall contact MSs directly to agree on the exact numbers of PLs to be distributed in line with the published Q&A on labelling flexibilities.

A QR code and URL printed on the outer carton, QR card and the PL will provide access to the package leaflet in the national language(s).

Moreover, the MAH shall contact MSs directly to agree on the exact numbers of PLs to be distributed in line with the published Q&A on labelling flexibilities.

The MAH shall provide a printed package leaflet in all EU languages by beginning 2022. The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned. The MAH shall also contact MSs directly to agree on the exact numbers of PLs to be distributed, again in line with the published Q&A on labelling flexibilities.

c) Outer and immediate labelling. Temporary omission of certain particulars on the labelling (from start of supply to end 2021).

The following exemptions are temporarily agreed for the outer labelling. These exemptions are justified on the necessity to label batches ahead of time.

Outer carton and printed package leaflet

- Common name: 'COVID-19 vaccine (Ad26.COV2-S (recombinant))' (initially proposed), instead of 'COVID-19 vaccine (Ad26.COV2-S [recombinant])' (agreed during evaluation [with square brackets]). This exemption on the common name is temporarily agreed for the outer carton and the printed package leaflet for the first batches until end 2021.

Outer carton

- Statement of the active substance. Due to the expedited development, product specifications were not final at the early stage of printing packaging materials. Therefore, the statement of active substance will be fully omitted from the outer carton for the first batches until end 2021.

- Abbreviated MAH name and company logo

d) EU Marketing Authorisation number (from start of supply to end 2021)

The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch to national variants of the EU packaging by beginning 2022. The MA number will be available on the electronic version of the EUPI.

e) Blue Box (from start of supply to end 2021)

Due to the use of one unified pack across all the EU countries, an exemption for the Blue Box has been

granted to omit it from the outer carton.

The information normally provided in the market specific packaging Blue Box area of the carton will be provided as an electronic version on the website (via the QR code/URL) under the country page, if required by the National Competent Authorities in each MS. The QR code and URL address (website) will be made available on the PL, carton box and QR card.

The Blue Box will be included in the updated carton component when national variants of the packaging will be possible by beginning 2022.

f) QR card (from start of supply to end 2021)

One QR card will be supplied in each carton box. The QR card will include a QR code and an URL address (website) that links to an electronic product information translated in all EU languages.

h) Manufacturers responsible for batch release (from start of supply to end 2021)

Due to the use of two manufacturers responsible for batch release for the supply of this vaccine in the EU, an exemption is requested for not indicating which is the manufacturer responsible for the release of the concerned batch in the printed package leaflet. This request is justified to meet capacity demands, and to ensure there is sufficient flexibility to accommodate for possible delays at some manufacturing sites or unavailability of release capacity.

Both manufacturers responsible for the batch release will be listed in the printed package leaflet. In addition, the following sentence: "*For the specific manufacturer of the vaccine you have received, check the Lot number on the carton or vial and please contact the local representative of the Marketing Authorisation Holder*." will be included in the package leaflet for traceability purposes.

Exemption from the obligation of serialisation

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack for a period of 3 months starting from the EC decision date.

- the MAH shall provide monthly progress reports on the serialisation: referring to details on the progress achieved in terms of ensuring compliance, e.g. proof of acquiring the relevant equipment, the date for the validation, the proof of contract to connect to the European Medicines Verification Organisation;

- the MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory;

- the MAH should also consider technical solutions to the serialisation due to the risk of falsification. The following safety features were endorsed:

- proprietary name Janssen varnish on via label and folding box;
- digital watermark on vial and folding box;
- hidden image on folding box;
- glues anti tamper evident flaps.

Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

Statutory information

- Approved regulatory information, including the patient information leaflet (PIL) and Summary of Product Characteristics (SmPC);
- Vaccination Card;
- Blue Box information as required by each Member State;
- Storage, dosing and administration brochure;
- Access to the national reporting systems for adverse events websites;
- Contact numbers for more information on the COVID-19 vaccine including product quality complaints;
- Link to the COVID-19 vaccine Janssen on the EMA website.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, COVID-19 Vaccine Janssen (adenovirus serotype 26 vector encoding sars-cov-2 spike glycoprotein (Ad26.COV2-S)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

Disease or condition

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

COVID-19 is a respiratory disease caused by the novel coronavirus SARS-CoV-2. The virus has spread worldwide during 2020, causing WHO to declare a pandemic in March 2020.

The virus infects the airways and causes a broad spectrum of respiratory symptoms ranging from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS) and ARDS. The pandemic is still ongoing despite unprecedented efforts to control the outbreak.

Available therapies and unmet medical need

COVID-19 case management has evolved during 2020 and includes, among others, anti-viral therapy and anti-inflammatory agents. In EU, remdesivir has been granted a conditional marketing authorisation for the treatment of COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kg) with pneumonia who require supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) based on positive results in some subgroups from clinical study NIAID-ACTT-1, in which remdesivir could speed up the recovery time with 4 to 6 days (Beigel 2020, EMA 2020b).

Dexamethasone can be considered a treatment option for adult and adolescent patients who require supplemental oxygen therapy based on published data from the RECOVERY study which showed a relative reduction in the number of deaths within 28 days of 35% compared to usual care in patients on invasive mechanical ventilation and 20% in patients receiving oxygen therapy without mechanical ventilation.

There remains an urgent public health need for the rapid development of novel prophylactic therapies, including vaccines, both for protection of particularly vulnerable groups as well as mitigating the effects of the pandemic on a population level. Several vaccine candidates are being developed and three of them (Comirnaty, COVID-19 Vaccine Moderna, and COVID-19 Vaccine AstraZeneca) were granted a conditional marketing authorisation in the EU. There is a very high global demand for suitable vaccines to help counteract the ongoing pandemic.

Main clinical studies

Five studies are ongoing with Ad26.COV2.S, of which 3 Phase 1/2 studies evaluate the immunogenicity and safety of Ad26.COV2.S and 2 large phase 3 trials evaluate the efficacy, safety, and immunogenicity of Ad26.COV2.S in adults. The first efficacy trial, VAC31518COV3001, is the pivotal study for this application.

The trial VAC31518COV3001 is a randomised, double-blind, placebo-controlled, Phase 3 study in adults ≥18 years of age conducted in the US, several Latin American countries (Argentina, Brazil, Chile, Peru, Mexico, Colombia), and South Africa. Participants were randomised in parallel in a 1:1 ratio to receive Ad26.COV2.S at a dose level of $5x10^{10}$ vp or placebo intramuscularly. Individuals are planned to be followed for up to 24 months. The trial design was revised after EUA in the US (on February 27, 2021) to offer Ad26.COV2.S vaccination within the trial (for participants who had received placebo), and unblinding of participants and investigators. All participants will be encouraged to remain in the study and continue to be followed for efficacy/effectiveness, safety and immunogenicity as originally planned for up to 2 years post-vaccination on Day 1.

A total of 43,783 randomised participants received the study vaccine (21,895 and 21,888 in the Ad26.COV2.S vs placebo arms). Randomisation was stratified by site, age group (≥18-<60 years of age vs ≥60 years of age), and absence/presence of comorbidities that are or might be associated with an increased risk of progression to severe COVID-19.

3.2. Favourable effects

Efficacy of Ad26.COV2.S for the co-primary endpoint 'moderate to severe/critical COVID-19' with an onset from Day 14 after vaccination was 66.9% (adjusted 95% CI: 59.03; 73.40) over a median follow-up time of 58.0 days, in seronegative individuals. For the co-primary endpoint 'moderate to severe/critical COVID-19' with an onset from Day 28 after vaccination, efficacy was 66.1% (adjusted

95% CI: 55.01; 74.80) over the same period, in seronegative individuals. The primary objective was met for both co-primary endpoints since the lower limit (LL) of the 95% CI of vaccine efficacy were above the pre-specified limit of 30%.

Number of cases and efficacy estimates were consistent when using the US FDA Harmonized (CDC) COVID-19 case definition or when using the endpoint 'symptomatic COVID-19' cases which include cases classified as either mild, or moderate to severe/critical (66.9% [95% CI: 59.07; 73.37] >14 days and 66.5% [95% CI: 55.50; 75.05] >28 days). There were very few mild cases, and the vast majority of 'symptomatic COVID-19' cases were thus captured by the primary endpoint. These data therefore support an indication against COVID-19 of any severity.

For this reason, 'COVID-19' is used in the SmPC section 5.1 to describe for the primary outcome of the study. It is considered misleading to use the exact primary endpoint of 'moderate to severe/critical COVID-19' as it could suggest that the cases corresponding to the primary endpoint were more severe compared to other vaccines' trials, which is not the case.

Efficacy against severe disease was demonstrated. Of the 116 vs. 348 primary endpoint cases with an onset at least 14 days after vaccination in the vaccine vs. placebo group respectively, 14 (12%) vs. 60 (17%) were classified as severe/critical (further referred to as severe, also in the SmPC). The point estimate of VE against severe disease was 76.7% (adjusted 95% CI: 54.56; 89.09) over a median follow up of 58 days, in SARS-COV-2 seronegative subjects. Of the 66 vs. 193 primary endpoint cases with an onset at least 28 days after vaccination in the vaccine vs. placebo group respectively, 5 (8%) vs. 34 (18%) were classified as severe. VE against severe disease was estimated at 85.4% (adjusted 95% CI: 54.15; 96.90) over the same follow-up period in seronegative subjects. Of the 14 vs. 60 severe cases with onset at least 14 days after vaccination in the Ad26.COV2.S group vs. placebo group, 2 vs. 6 were hospitalised. Three died (all in the placebo group). Most of the remaining cases only fulfilled the oxygen saturation (SpO2) criterion for severe disease ($SpO2 \leq 93\%$). For many cases this was based on self-measured abnormal oxygen saturation episodes (at home). During the COVID-19 event, at least one measurement was taken by the investigator's site or by a home visit by investigator's personnel. All cases were adjudicated by an independent committee of clinical experts.

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

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

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

In the PP analysis set, 40% of the participants had at least one comorbidity, the most common being obesity (BMI ≥30 kg/m2, 28%), hypertension (10%) and type 2 diabetes mellitus (7.5%), followed by serious heart conditions (2.5%), HIV infection (2.5%), asthma (1.5%), COPD (1%). It should be noted that only participants with stable conditions were enrolled. Efficacy against molecularly confirmed 'moderate to severe/critical COVID-19' was observed both in participants with and without comorbidities with point estimates respectively of 62.9% and 69.1% for cases with onset at least 14 days after vaccination, and 48.6% and 72.6% for cases with onset at least 28 days after vaccination.

Efficacy against molecularly confirmed 'moderate to severe/critical COVID-19' was demonstrated in each participating country. Except for South Africa, all point estimates were >65% for events with onset at least 14 days after vaccination (not computed in Chile and Mexico due to small numbers of cases).

In South Africa, vaccine efficacy was of lower magnitude compared to other regions/countries (39.6% [95% CI: 8.77; 60.46] for cases with onset at least 14 days and 57.3% [95% CI: 26.51; 76.03] for cases with onset at least 28 days after vaccination). Heterogeneity across regions was much less marked when considering the PCR positive cases from any source (including those not yet confirmed by the central laboratory) (South Africa: 52.0% [95% CI: 30.26; 67.44] for cases with onset at least 14 days, 64.0% [95% CI: 41.19; 78.66] for cases with onset at least 28 days after vaccination). Higher vaccine efficacy estimates were determined against severe disease (secondary endpoint). In the extended data set, when considering cases with onset at least 14 days after vaccination, the VE against severe COVID-19 was consistently high, including in South Africa (73.1% [95% CI: 40.03; 89.36] compared to 78.0% [95% CI: 33.13; 94.58] in the US and 89.1% [95% CI: 17.0; 98.0] in Brazil). When evaluated at least 28 days after vaccination, VE point estimates were above 81.7% and comparable between South Africa, the US and Brazil Colombia.

The applicant has characterised the virus from 71.7% of the cases and it was found that, for South Africa, 94.5% of the sequences corresponded to the 20H/501Y.V2 variant (B.1.351 lineage, which shows 9 aminoacid differences and a deletion of two aminoacids in the S protein as compared to the strain included present in the vaccine), in Brazil 69.4% of the sequences corresponded to the variant from the P.2 lineage and 30.6% to the Wuhan-Hu1 reference sequence+D614G variant, whereas in the USA 96.4% of the sequences corresponded to the Wuhan-Hu1 reference sequence+D614G. As there were predominant variants in the USA and South Africa, VE in those countries are likely to reflect the efficacy against the respectively circulating variants. These results predict high vaccine efficacy in case the South-African variant 20H/501Y.V2 spreads globally.

Ad26.COV2.S elicited both humoral (close to 100% seroconversion) and cellular immune responses in vaccinated subjects, as early as 14 days post-vaccination, in both young and older adults.

3.3. Uncertainties and limitations about favourable effects

Duration of protection beyond 8 weeks is not known. Efficacy data are not available after this timepoint. Long-term vaccine efficacy data will become available from post-authorisation effectiveness studies and from the ongoing clinical trials. However, participants in the placebo arm are being unblinded and offered vaccination following the FDA EUA for this vaccine. Therefore, it is unclear whether robust efficacy data can be generated. Preliminary immunogenicity results from the FIH trial demonstrated antibody persistence up to 3 months post-vaccination. Whether antibody titers will persist over a longer period of time is not known. Also, to date, no immunological correlate of protection has been established.

Whether efficacy is higher against severe cases compared to all symptomatic cases is not confirmed yet, but there is a trend in that direction. Data suggest that efficacy point estimates tend to increase with the degree of severity of the case definition. For the severe COVID-19 case definition efficacy was 76.7% and 85.4%, while for the moderate COVID-19 case definition efficacy was 64.8% and 62.0%, respectively after 14 days and after 28 days.

The efficacy was demonstrated in the overall participants aged 18 years and older, and in participants ≥65 years. However, the number of cases in individuals aged 75 and older at highest risk of severe COVID-19 is limited. No COVID-19 cases were detected in individuals aged ≥80 years. As baseline

frailty status was not assessed, no information on efficacy data in frail subjects was obtained. Long term health care residents were not studied for this application.

Efficacy was demonstrated in trial participants with and without comorbidities. Point estimates tend to be lower in participants with comorbidities, but the 95% CIs are overlapping. When considering efficacy after 28 days, when the numbers of events are the lowest, for the older participants with comorbidities, the lower limit of the 95% CI was <0. For cases with onset at least 28 days post-vaccination, vaccine efficacy was 33.2% (95% CI: -77.59; 76.33) for participants ≥60 years and 44.0% (-85.99; 85.26) for participants ≥65 years. The 95% CI are very wide as estimates are based on few events. At this stage it is not considered that there is an efficacy concern in individuals with comorbidities. Given the nature of the comorbidities (i.e. no immunocompromised participants), there is low biological plausibility for a significantly low efficacy in these study participants. Nevertheless, efficacy by age and comorbidities will need to be assessed over a longer FU time to generate more robust estimates.

Data are lacking in individuals with uncontrolled underlying disease and in those with several underlying diseases. Efficacy could not be assessed in participants with ≥3 comorbidities due to the limited number of cases.

There is no data on immunocompromised persons due to condition or immunosuppressive therapies. The applicant is planning an immunogenicity trial in immunocompromised participants as described in the RMP. Considering the lack of an immunological correlates of protection (ICP) and the heterogeneous nature of the various types of immune deficiencies, only some of which may impact on the immune response to a specific type of vaccine, the applicant is recommended to discuss the study design with competent authorities prior to study start.

Findings related to asymptomatic cases are preliminary since Day 71 samples were available for 6% of the FAS seronegative population. After 28 days post-vaccination, efficacy was 59.7% (95% CI: 32.75; 76.64) for the prevention of undetected/asymptomatic COVID-19 based on seroconversion to the SARS-COV-2 N protein and/or on positive PCR. Of the undetected/asymptomatic cases, most of the cases were ascertained based on seroconversion. These preliminary data are promising, as they suggest efficacy against asymptomatic SARS-COV-2 infection, at a level that may be consistent with efficacy against symptomatic disease.

Preliminary data suggest no impact of vaccination on upper respiratory tract viral load levels and duration of virus shedding in COVID-19 breakthrough cases, but this finding will need to be confirmed when the whole data set will become available.

It is not known if the vaccine prevents reinfection in those who are SARS-COV-2 seropositive at baseline, because efficacy could not be estimated as the number of cases was very low. Of 4,156 participants SARS-CoV-2 seropositive at baseline, 7 COVID-19 cases were reported as PCR positive from any source (3 vs. 4 in the active vs. placebo group after Day 14) of which one was confirmed by the central laboratory. However, efficacy is anticipated in this group. The immunogenicity data, albeit limited, support this assumption.

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

An analysis of efficacy per variant was not performed. However, efficacy was demonstrated in South Africa where the South African variant 20H/501Y.V2 was predominant. Efficacy was demonstrated in Brazil, but there was no predominant variant in Brazil. Two third of the cases may be attributable to the P.2 lineage. Spike sequence data were available for only 70% of the cases and a higher proportion of samples were sequenced in the placebo group as compared to the vaccine group, which could lead

to biases. An analysis of vaccine efficacy per SARS-CoV-2 variant is planned upon completion of the sequencing.

Preliminary data showed that neutralising antibodies elicited by Ad26.COV2.S were able to neutralise the B.1.1.7 lineage variant in vitro, although less efficiently than the reference strain. Thus, some protection against this variant too is anticipated.

More data should be generated post-authorisation to continue assessing vaccine efficacy against these variants. The extent and the onset of cross-protection against other relevant circulating or newly emerging strains of SARS-CoV-2 is unknown and should be investigated post-authorisation.

Ad26 seroprevalence varies across regions, with higher seroprevalence reported in Africa. In Europe seroprevalence is around 12%. Preliminary results of the COVID-19 program do not indicate a major impact of pre-existing Ad26-nAb on the vaccine-induced SARS-CoV-2 S protein binding Ab responses, but this issue needs to be followed up post-authorisation.

3.4. Unfavourable effects

The assessment of Ad26.COV2.S safety is based on the Phase 3 study COV3001 (up to the cut-off date of 22 January 2021), comprising 43,783 participants who received either a single dose of Ad26.COV2.S at $5x10^{10}$ vp (21,895 adults) or placebo (21,888 adults) (FAS). Reactogenicity data were collected in a subset of 6,736 participants who received either vaccine (3,356 adults) or placebo (3,380 adults) (Safety subset). Information on unsolicited AEs was collected for 28 days after vaccination, information on AESIs and SAEs is collected for the entire study duration. At the time of the primary analysis, the median follow-up after vaccination was 58 days in both groups.

Any solicited local and systemic AEs were reported more frequently in Ad26.COV2.S than in the control group (66% and 41.9% of evaluated participants respectively, within the first 7 days following injection). The most frequently reported solicited local AE after Ad26.COV2.S vaccination was injection site pain (48.7% vs. 16.7%, respectively). The most frequently reported solicited systemic AEs were headache (39% in Ad26.COV2.S group vs. 23.8% in the placebo group), fatigue (38.3% vs. 21.6%, respectively), and myalgia (33.2% vs. 12.8%). Pyrexia was reported in 9.0% participants in the Ad26.COV2.S group (vs. 0.6% of participants in the placebo group). Most solicited AEs were transient and self-timing. Overall, the median duration of the selected solicited AEs was similar in both groups (1 to 2 days after vaccination), and also the median time to onset (within 1 to 3 days after vaccination). Solicited adverse events were mainly grade 1 or 2. The frequency of Grade 3 solicited AEs was low overall, but higher in participants in the Ad26.COV2.S group (2.2%) compared to participants in the placebo group (0.7%). There was no grade 4 solicited AEs.

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

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

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

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

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

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

There were 3 cases of Bell's palsy (facial paralysis) in the Ad26.COV2.S group (2 SAE considered as possibly related SAEs by the investigator, but not related by the Sponsor; and 1 non-related AE) compared with 2 cases in the placebo group (non-related). Based on data from reported events, a causal relationship between Ad26.COV2.S vaccination and Bell's palsy could not be confirmed nor ruled out (at least 2 cases possibly related to the vaccine). Bell's palsy is included in the list of AESIs subject to routine and additional pharmacovigilance activities, but not in the SmPC as there is no clear imbalance vs. placebo.

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

Asthma was reported for 7 participants in the Ad26.COV2.S group versus 1 participant in the placebo group, although most were unrelated to study treatment . In the Respiratory, thoracic and mediastinal

[8] includes one event reported as venous thrombosis limb and one event reported as embolism venous

disorders, 10 subjects reported 10 SAEs in the Ade26.COV2.S group (3 Pulmonary embolism, 2 Dyspnoea, 2 Hypoxia, 1 Chronic obstructive pulmonary disease, 1 Pleural effusion, 1 Pneumothorax spontaneous) compared to 4 subjects reporting 6 SAEs in the placebo group (Pulmonary embolism, Dyspnoea, Cough, Oropharyngeal pain, Respiratory distress, Respiratory failure). Although the causality is not clear, because there is an imbalance in the number of cases vs. placebo, the risk of exacerbation of chronic pulmonary disorders (i.e. asthma and COPD) might be further monitored in the planned PASS as an AESI (pending feasibility assessment that will be included in the draft protocol).

3.5. Uncertainties and limitations about unfavourable effects

At the time of the primary analysis, the median follow-up after vaccination was 58 days in both groups. Longer safety follow-up of >2 months is available for 23,903 participants in the FAS: 11,948 participants in the Ad26.COV2.S group (54.6%) and 11,955 in the placebo group (54.6%). However, only 34 participants in the Ad26.COV2.S group (0.2%) and 31 in the placebo group (0.1%) have been followed for up to 4 months. Long-term safety data is not yet available and will be characterised as part of the continuation of the pivotal clinical trial, other trials and a PASS.

No safety issues were identified in vaccinated seropositive subjects, however, due to the limited number of subjects in the safety subset, no definitive conclusions can be drawn (154 in the Ad26.COV2.S group and 147 in the placebo group).

There is no data in immunocompromised individuals, including those receiving immunosuppressant therapy, thus the safety of Ad26.COV2.S in these individuals will be evaluated post-authorisation as described in the RMP.

There is only very limited clinical experience in pregnant women with Ad26.COV2.S (4 exposed pregnant women). However, there were a significant number of pregnancy cases (1,631) reported for the Ad26 platform safety data (cut-off 21 December 2020; mainly from Ebola vaccine trials N=1,522) of which 280 were exposed during the first trimester). In addition, data from non-clinical studies do not indicate any harm during pregnancy. In the absence of clinical data with Ad26.COV2.S to confirm the favourable profile seen with other antigens, risks during pregnancy remains theoretical. Considering the Ad26 vector is a non-replicating vector, and considering the small amount that is administered intramuscularly, it is deemed unlikely that this vaccine may pose a specific risk during pregnancy, apart from the risk that may be associated with a fever-reaction. Use of Ad26.COV2.S in pregnant women will be investigated in the planned PASS.

Although, in COV3001, up to the cut-off date of 31 December 2020, 128 breastfeeding women were enrolled in Ad26.COV2.S group, no data on shedding in breastmilk was collected during the study. Use in breastfeeding women will be investigated via a PASS.

The available data (non-clinical, clinical, neutralising capacity of antibodies) do not raise a concern regarding vaccine-associated-enhanced disease for the time being. However, the possibility of enhanced disease cannot be excluded with certainty. The RMP lists VAED (including vaccine-associated enhanced respiratory disease - VAERD) as an important potential risk to be followed up post-authorisation.

Co-administration with other vaccines was not studied, but a co-administration study of Ad26.COV2.S with seasonal influenza vaccine is planned.

In the COV3001 FAS, there were 21,895 adults ≥18 years of age, including 809 adults ≥75 years of age (3.7%), of which 495 adults had comorbidities (2.3%), and 8,936 adults with comorbidities (40.8%), of which 2,271 adults were ≥65 years of age(10.4%). Frailty has not been evaluated yet. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease COPD,

diabetes, chronic neurological disease, cardiovascular disorders) will be investigated via the ongoing study COV3001 and in the planned PASS.

3.6. Effects Table

Table 36. Effects Table for COVID-19 Vaccine Janssen intended for active immunisation to prevent COVID-19 caused by SARS-CoV-2 (data cut-off: 22 January 2021)

	Short Description	Unit	Ad26.COV2.S	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Vaccine efficacy overall -**14 days**	First occurrence of moderate to severe COVID-19 with onset at least 14 days post-vaccination, **any age**	**VE (%)** (95% CI)	**66.9** (59.03, 73.40)		**SoE**: Robust data showing vaccine efficacy after 14 days and 28 days and are further supported by the different secondary endpoints after 14 and 28 day **SoE**: Efficacy observed in the elderly (≥65yoa) **SoE**: Efficacy observed in participants with various comorbidities **Unc**: Short median FUP of 58 days	Study VAC31518COV3001
		n cases/ n subjects at risk for the endpoint	**116**/ 19,630	**348**/ 19,691		
	≥65 years of age	**VE (%)** (95% CI)	**82.4** (63.90, 92.38)			
		n cases/ n subjects at risk for the endpoint	**9**/ 3,984	**51**/ 4,018		
Vaccine efficacy overall - **28 days**	First occurrence of moderate to severe COVID-19 with onset at least 28 days post-vaccination, **any age**	**VE (%)** (95% CI)	**66.1** (55.01, 74.80)			
		n cases/ n subjects at risk for the endpoint	**66**/ 19,630	**193**/ 19,691		
	≥65 years of age	**VE (%)** (95% CI)	**74.0** (34.40, 91.35)			
		n cases/ n subjects at risk for the endpoint	**6**/ 3,984	**23**/ 4,018		
Vaccine efficacy against **severe COVID-19**	First occurrence of severe COVID-19 with onset at least **14 days** post-vaccination.	**VE (%)** (95% CI)	**76.7** (54.56, 89.09)			
		n cases/ n subjects at risk for the endpoint	**14**/ 19,630	**60**/ 19,691		
	First occurrence of severe COVID-19 with onset at least **28 days** post-vaccination.	**VE (%)** (95% CI)	**85.4** (54.15, 96.90)			
		n cases/ n subjects at risk for the endpoint	**5**/ 19,630	**34**/ 19,691		

	Short Description	Unit	Ad26.COV2.S	Placebo	Uncertainties/ Strength of evidence	References
Unfavourable Effects*						
Headache	Solicited systemic AEs	% of individuals reporting the ADRs	39.0	23.8	Transient effect, majority mild to moderate in severity ADRs milder and reported much less frequently in older adults (≥ 65 years old). ADRs reported more frequently in females compared to males.	Study COV3001 (cut-off 22/01/2021) – safety subset
Fatigue			38.3	21.6		
Myalgia			33.2	12.8		
Nausea			14.2	9.7		
Pyrexia			9.0	0.6		
Injection site pain	Solicited local AEs		48.7	16.7		
Injection site erythema			7.3	3.9		
Injection site swelling			5.3	1.6		
Chills	Unsolicited AEs		2.0	0.6		
Arthralgia			1	0.7		

Abbreviations: ADR: adverse drug reaction, SoE: strength of evidence
Notes:
*only the most frequently reported adverse reactions are listed. For a full summary of all adverse reactions refer to the Summary of Product Information section 4.8.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, the efficacy of a single dose of Ad26.COV2.S at a dose level of $5x10^{10}$ vp has been demonstrated for the prevention of symptomatic COVID-19 in adults ≥18 years of age, as well as an acceptable safety profile, based on the large pivotal phase 3 trial included in this MAA.

The results are considered robust based on the study design and are further supported by the different secondary endpoints and analyses.

Ad26.COV2.S has been shown to protect against severe disease.

Subgroup analyses of the primary efficacy endpoint showed efficacy for elderly (≥65 years), as well as for participants with medical comorbidities associated with high risk of severe COVID-19, which is considered as the population at highest need for preventative strategies.

Efficacy against COVID-19 was demonstrated in each participating country, including South Africa (where the variant of concern 20H/501Y.V2 was the predominant circulating strain during the study), although efficacy was of lower magnitude compared to other region/countries.

The main shortcoming of the current efficacy dataset is the unusually short median follow up of approx. 58 days, but longer-term data will be submitted post-authorisation as detailed in the specific obligation and recommendations. More data will be generated post-authorisation to further characterise longer term protection. In the current situation this gap in knowledge is outweighed by urgent need, high COVID-19 disease burden, and limited availability of preventative and therapeutic remedies.

It would be desirable to confirm if this vaccine also has an effect on asymptomatic infection and viral transmission. These aspects cannot be evaluated fully based on clinical trials data and will likely be further elucidated through effectiveness studies post-authorisation.

The observed safety profile is considered well characterised and acceptable based on the short-term data available. The safety of Ad26.COV2.S is mainly characterised by local and systemic reactions occurring during the first 7 days after vaccination. Reactions were mostly mild to moderate, transient and self-limited. The reactogenicity was milder and lower in older adults aged ≥65 years compared to the younger adults aged ≥18 to 64. SAEs and AESIs were infrequent in the Ad26.COV2.S and placebo groups.

Long term safety has to be characterised further, and it is important to analyse the full year safety follow-up of the ongoing trials. The current dataset gives no indication of vaccine-enhanced disease, a potential risk that should be followed up as detailed in the RMP.

There is limited clinical experience in pregnant women with Ad26.COV2.S, but a significant experience was accumulated with the Ad26 platform. In addition, preliminary preclinical data are reassuring; therefore, noting that pregnancy as such is a risk factor for severe COVID-19, that pregnant women may additionally belong to other risk groups, and that a protective effect is anticipated, vaccination may be considered on a case by case basis. Data in pregnancy will be generated post-authorisation, as detailed in the RMP. Although breastfeeding women were included in the clinical studies with Ad26.COV2.S, there are no data available. However based on biological plausibility, no risk in vaccinating breast-feeding women is anticipated.

Immunocompromised individuals were excluded from the efficacy trial. Some immunocompromised individuals may not be protected as well as immunocompetent individuals by vaccination. However, no safety issues are anticipated, and the B/R balance in immunocompromised subjects is deemed positive, also in light of the underlying excess risk of COVID-19. Further data will be collected post-authorisation as detailed in the RMP. Also, subjects with severe underlying diseases were not included in the studies, and the safety and effectiveness of the vaccine in these groups will be followed up post-authorisation as detailed in the RMP.

Regarding seropositive subjects, no safety issues have been observed in this population, and efficacy can be anticipated. Therefore, the vaccine can be administered without performing previous SARS-CoV-2 serology testing.

3.7.2. Balance of benefits and risks

Given the demonstrated favourable effect and considering the overall characteristics of the unfavourable effects, a positive B/R balance in the proposed indication is concluded.

3.7.3. Additional considerations on the benefit-risk balance

Given the current emergency situation, it is considered that the identified uncertainties could be addressed post-authorisation through specific obligations, including the continuation of the pivotal

clinical study as long as possible, and post-approval effectiveness studies and routine safety surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of the vaccine.

The active substance and finished product are acceptable in relation to control of critical quality attributes and impurities.

Studies to demonstrate batch-to-batch consistency of the finished product in terms of process validation studies/process performance qualification studies (PPQ) have not been fully completed in the finished product commercial manufacturing site Catalent Indiana. Nonetheless, sufficient data have been provided for full scale lots (including some PPQ lots) at the commercial sites and at other sites using the commercial process.

Considering the above and the current public health emergency, the information provided on the manufacturing of the finished product is considered acceptable. Nevertheless, in order to confirm the consistency of the finished product manufacturing process, the applicant should provide the completed process validation (including hold times) and comparability data for the Catalent Indiana site as a post-approval specific obligation. It is considered likely that the applicant will be able to provide the requested data and thereby fulfil the specific obligation.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete the proposed specific obligation.

Based on the applicant's plans and documentation, it is expected that data to fulfil the quality SO will be submitted gradually between March and August2021.

Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomised, placebo-controlled study COV3001 to obtain 2-year long-term data and to ensure sufficient follow-up to confirm the efficacy and safety of COVID-19 Vaccine Janssen. The completion of the Phase 3 study COV3001 will lead to comprehensive date on the efficacy and safety of COVID-19 Vaccine Janssen.

- Unmet medical needs will be addressed, as

There is an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19. Currently there are two mRNA vaccines and a monovalent vaccine composed of chimpanzee adenovirus encoding the SARS CoV-2 spike glycoprotein (ChAdOx1-S) approved in the EU to prevent COVID-19.

Despite the recent granting of a conditional marketing authorisation for Comirnaty, COVID-19 Vaccine Moderna, and COVID-19 vaccine AstraZeneca, there is still an urgent need to provide additional prophylactic options in the context of the pandemic across the EU.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The demonstrated efficacy and the satisfactory safety profile support the immediate availability of the product in the current emergency setting, notwithstanding the outlined uncertainties.

3.8. Conclusions

The overall B/R of COVID-19 vaccine Janssen is positive.

Eligibility to a conditional marketing authorisation as well as fulfilment of the requirements have been demonstrated in line with provisions of Article 14-a of Regulation (EC) No 726/2004.

4. Recommendations

4.1. Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of COVID-19 vaccine Janssen is favourable in the following indication:

> *COVID-19 Vaccine Janssen is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals18 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations*

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

4.2. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

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

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

Description	**Due date**
In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation and comparability data.	15 August 2021 Interim report: 31 March 2021
In order to confirm the efficacy and safety of Ad26.COV2.S COVID-19 vaccine, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	31 December 2023

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S) is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Annex I – List of Recommendations (RECs)

Area	Number	Description	Classification*	Due date
Active Substance				
Quality	1	The MAH should provide the validation data of the third process validation inoculum batch produced at Janssen Biologics B.V. (Leiden, NL).	REC	Q4-2021
Quality	2	The MAH should provide the tier 2 comparability data to confirm that the large scale AS (from Janssen Biologics B.V., Leiden, NL) is comparable to the small scale process material (from Janssen Vaccines and Prevention B.V., Leiden, NL).	REC	30 June 2021
Quality	3	The MAH should provide the tier 2 comparability data to confirm that the large scale AS (from Emergent, USA) is comparable to the AS from the other commercial AS sites.	REC	31 July 2021
Quality	4	The MAH is requested to initiate stability studies (including representative lots) for the large scale AS process at Emergent (USA). In addition, for each new AS manufacturing site, AS stability studies should be initiated. The applicant is requested to provide the AS stability data for representative AS batches for each manufacturing scale (small scale at the Janssen Vaccine and Prevention site B.V. (Leiden, NL) and large scale batches produced at the Janssen Biologics B.V. (Leiden, NL)) when the respective studies have been finalised and the results are available.	REC	Q2-2024
Finished Product				
Quality	5	The MAH should provide the following updated sections for the second FP site: 3.2.P.3.5 Process Validation and/or Evaluation – Depyrogenation of Glass Vials, 3.2.P.3.5 Process Validation and/or Evaluation – Sterilisation of Equipment Components and Stoppers, and 3.2.P.3.5 Process Validation and/or Evaluation – Decontamination of Filling isolators.	REC	31 March 2021

Quality	6	The MAH should provide the tier 2 comparability data to confirm that FP from the first FP site can be considered comparable to the Phase 3 clinical FP lots.	REC	30 June 2021
Quality	7	Regarding the process validation of the first FP site, the MAH should provide the results from bulk homogeneity verification during formulation and sterile filtration and filling by 31 July 2021. In addition, the additional characterisation data to confirm the hold times should be provided.	REC	31 July 2021
Quality	8	To evaluate the sensitivity of Ad26.COV2.S FP when exposed to light stress, a study based on the ICH Q1B requirement should be performed. The samples should be tested for potency, turbidity, radius and aggregation.	REC	30 September 2021
Quality	9	The MAH should provide an updated section 3.2.P.2.3 Manufacturing Process Development – Comparability, including results from forced degradation studies using thermal stress conditions (which were performed as part of the comparability analysis between clinical Phase1/2 lots and phase 3 lots).	REC	30 June 2021
Quality	10	A final conclusion on the criticality of the potentially critical parameters in an updated version of section 3.2.P.2.3 Manufacturing Process Development – Control Strategy Development – Critical Process Parameters should be provided. In addition, the MAH should provide an updated table 1 Summary of Critical Process Parameters and Associated PAR in FP Manufacturing Process in 3.2.P.2.3 Manufacturing Process Development – Control Strategy Development – Critical Process Parameters.	REC	31 July 2021
Quality	11	The MAH should provide the results of the 6 month time point of the FP container leachables study.	REC	31 December 2021

Quality	12	Regarding the FP specification for polydispersity, the MAH should establish and justify acceptance criteria once sufficient experience and data for this parameter are available.	REC	31 December 2021
Quality	13	The MAH should provide a summary of the risk assessment of elemental impurities in the Ad26.COV2.S finished product to confirm compliance to ICH Q3D Guideline.	REC	31 March 2021
Quality	14	The MAH should provide the FP stability data for the 3 FP PPQ batches from the first FP site when the stability studies have been finalised and the results are available (by Q2 2024). In addition, for each additional FP manufacturing site, FP stability studies should be initiated.	REC	As soon as possible
Clinical immunogenicity and efficacy– final cMAA - REC				
Clinical	15	The MAH is requested to provide the validation report of the SARS-CoV-2 microneutralisation assay (WT-MNA), which would include an external validation with international reference standard material.	REC	As soon as possible
Clinical	16	The MAH is requested to test the in-house developed S protein-ELISA with international reference standards and provide the results.	REC	As soon as possible
Clinical	17	With results submission obtained with the N protein-ELISA, the MAH is requested to give clarification on how the data were interpreted.	REC	As soon as possible
Clinical	18	The MAH is requested to provide validation reports IFN-γ and IL-4 ELISpot assays with final CSR	REC	As soon as possible
Clinical	19	Regarding the CD4 and CD8 Th1 immune responses induced following vaccination in study VAC31518COV1001 and VAC31518COV2001, the MAH is requested to provide median of responses based on positive samples only and comparison between group in the final CSR.	REC	As soon as possible

Clinical	20	The MAH is requested to discuss if the qualification (and validation) results of the initial WT-MNA could be generalised to MNA based assay using different strains and/or whether this will be addressed.	REC	As soon as possible
Clinical	21	The MAH is requested to provide data on cross-neutralisation for clinically relevant and emerging SARS-CoV-2 strains by testing sera of human clinical participants (particularly of study VAC31518COV3001 in functional in vitro assays).	REC	As soon as possible
Clinical	22	The applicant is requested to present the plan regarding the assessment of the vaccine performance against emerging variants and/or performance of a new vaccine construct (including the Spike protein from a variant of concern) in protecting against COVID-19 if it appears that a new construct vaccine is needed in the future.	REC	As soon as possible
Clinical	23	The MAH should justify why, in study VAC31518COV2001, the anamnestic response will be assessed after a shorter interval between the primary vaccination and the antigen presentation for the 2-dose schedule when compared to the 1-dose schedule (final CSR).	REC	As soon as possible
Clinical	24	The MAH is requested to present the data on (and discuss) the impact of the natural and vaccine-induced immunity to the Ad26 vector on the insert-specific vaccine-induced immune responses by COVID-19 study, overall for the COVID-19 program and overall for Ad26-based vaccination. In addition, the population of COV3001 should be described according to baseline immunity to the vector. The applicant should provide this data in the final CSR.	REC	As soon as possible
Clinical	25	For study COV3001, the MAH should provide the baseline comorbidities leading to higher risk of severe disease of the subjects included in the immunogenicity subset and of those included in the subset used for the additional binding Ab analysis (or any other analysis).	REC	As soon as possible
Clinical	26	For study COV3001, the MAH should present the plan on the immune correlate of protection and provide results when available.	REC	As soon as possible

Clinical	27	For study COV3001, the MAH should provide plans to address waning of immune responses and vaccine efficacy, and the need for and timing of booster, in the context of crossover vaccination and resulting loss of placebo-controlled follow up. Provide SAP including these plans (including analyses at 6 months FU and before cross-over). The applicant is recommended to seek further interaction via EMA Scientific Advice on these points.	REC	As soon as possible
Clinical	28	For study COV3001, the MAH should provide cross-tabulation data linking seroconversion and RT-PCR results, for the various case definitions (symptomatic, mild, moderate to severe/critical COVID-19).	REC	As soon as possible
Clinical	29	For study COV3001, the MAH should provide validation document of whole genome sequencing assay.	REC	As soon as possible
Clinical	30	For study COV3001, the MAH is planning an immunogenicity trial in immunocompromised (IC) participants. Considering the lack of an ICP, and the heterogeneous nature of IC populations, the MAH is recommended to seek EMA Scientific Advice on the study design	REC	As soon as possible
Clinical	31	For study COV3001, there are differences in terms of follow up duration affect the comparisons of efficacy across age groups and across participants with/without comorbidities. Differences in terms of timing of vaccination could also affect the interpretation of certain subgroup analyses (given the emergence of variants for which efficacy could vary). The MAH needs to provide analyses (such as stratified/adjusted) taking account of these factors for an appropriate interpretation of the subgroup analyses. A discussion is expected, including an analysis of the biases that could have affected the subgroup analyses.	REC	As soon as possible
Clinical	32	For study COV3001, a detailed description of the cases found in seropositive participants, including genomic analysis, is expected in the final report to ensure an accurate assessment of the cases. Without details, whether these cases were real re-infection or rather re-detection cannot be assessed. Any relevant information should be included in a table for	REC	As soon as possible

		each case, such as time of onset, age, country, genome sequencing etc.		
Clinical	33	For study COV3001, when submitting updated data on asymptomatic cases as part of a further report, the MAH should present these data by variant, and include a discussion on the sources of biases (such as biases related to varying efficacy and clinical expression of disease across variants, differences in terms of follow up duration for the assessments of the endpoint).	REC	As soon as possible
Clinical	34	For study COV3001, in addition to the planned endpoint 'asymptomatic or undetected COVID-19' based on PCR and seroconversion to the N protein, the analysis used an endpoint based on 'seroconversion only'. An endpoint considering all seroconversions to the N protein (irrespective of the PCR result) appears more relevant and should be presented as well.	REC	As soon as possible
Clinical	35	For study COV3001, in the final CSR, the MAH should present the concordance between PCR results and seroconversion for the N protein serology, in symptomatic and asymptomatic cases with PCR results available (from the central lab, and from any source).	REC	As soon as possible
Clinical	36	In study COV3001, to assess the impact of excluding subjects with missing SARS-CoV-2 serology status at baseline, a sensitivity analysis of VE on subjects seronegative at baseline only should be performed.	REC	As soon as possible
Clinical	37	The MAH should submit the 6 month and 1 year interim Clinical Study Reports for the randomised, placebo-controlled, observer-blind study VAC31518COV3001.	REC	As soon as possible
Clinical	38	The MAH should submit the 6 month and 1 year interim and final Clinical Study Reports for the randomised, placebo-controlled, observer-blind study VAC31518COV3009.	REC	As soon as possible
Safety – final cMAA				
Clinical	39	The next version of the Adenoviral Vaccine Safety Database (V6.0) should be submitted including a discussion of the potential increased risk of HIV acquisition in individuals vaccinated with adenovirus-based vaccines (considered as an important potential risk) with a review of	REC	Expected for approx. April 2021

		reported cases in the updated Ad26 platform data.		
Clinical	40	Updated reports presenting the cumulative review of SAEs, pregnancy data, and neuroinflammatory adverse events with the Ad26 platform data should be submitted in 6 months.	REC	September 2021
Clinical	41	The MAH should evaluate the feasibility of including "Exacerbation of chronic pulmonary disorders (ie, asthma)" as an endpoint in study VAC31518COV4003, and the results should be provided as available. (a soon as available)	REC	As soon as possible
Safety– RR1 – REC. The applicant is recommended to submit, to support the development of future Ad26 vaccines, an updated Advac report integrating the data from the COVID-19 vaccine. Several points to consider in this future report are raised below				
Clinical	42	Baseline characteristics: Imbalance between groups were observed the AdVac safety database V5. In particular, differences have been noticed for region and ethnicity. In the Ad26 vaccination and placebo groups, respectively 37% and 52.2% of the subjects were from North America, and 26% and 9.5% from West Africa. Moreover, there were 34.8% white subjects in the Ad26 vaccination group and 48.5% in the placebo group; and 60.3% black or African American subjects in the Ad26 vaccination group and 46.8% in the placebo group. In further reports, this should be explained and impact on the results should be discussed. Immunity to the vector should be presented across groups, and any imbalance should be discussed.	REC	
Clinical	43	In the AdVac safety database V5, safety data have been provided irrespective of dose level and per subject (cumulating AE after all doses). In further reports, the applicant is recommended to provide the solicited AEs data for dose level $5x10^{10}$ and separately for other dose levels. Data should be presented separately, after dose 1 and after dose 2 (compared to placebo).	REC	
Clinical	44	High differences of frequency of solicited local and systemic AE have been reported depending of the insert. These differences are difficult to interpret given the confounding effect of several factors which could influence reactogenicity.	REC	

		Overall, the frequency of solicited local and systemic AEs tended to be lower in individuals with pre-existing Ad26 VNA positivity at baseline compared those without pre-existing Ad26 VNA positivity at baseline, but again the independent effect of immunity to the vector is unclear. There were also differences in reactogenicity profile across regions and age categories. In further reports, the applicant should list the factors that could influence reactogenicity and provide local and systemic solicited AE stratified for these factors, to allow for a better understanding of the independent influence of insert, pre-existing immunity to the vector, and other factors on reactogenicity.		
Clinical	45	The frequency of solicited AE local and systemic is generally much lower in West Africa than in other regions (East and Southern Africa, North America, Europe, and Asia), both for the active and placebo groups. Other differences were noted between African and other regions, such as that in the 3 African regions, no consistent difference between groups was observed as in America, Europe, and Asia. Moreover, in Ad26 individuals, the frequency of severe solicited systemic AEs (all, and related solicited systemic AEs) was lowest in East, West and Southern Africa compared to the other 3 regions. Regional differences in safety were already noted in the Zabdeno EPAR. At that time, the applicant argued that cultural differences may explain the differences in reporting rates of AEs across countries and regions. Discrepancies across regions could also reflect differences in terms of pre-existing immunity to Ad26 (higher in Africa) and methodological differences between studies. These discrepancies across regions should be discussed in further reports.	REC	
Clinical	46	In the AdVac safety database v5, the applicant stated that "solicited local and systemic AEs were generally collected from the day of vaccination until 7 days after each vaccination for all populations studied", and "unsolicited AEs were collected up to 28-30 days/4 weeks post-vaccination in most studies". This should be clarified in further reports. If any differences across studies/programmes, they should be	REC	

		described. In addition, the applicant should provide information on the duration of studies.		
Clinical	47	In the AdVac safety database V5, only limited clinical safety data, and brief conclusions have been given for adults ≥60 years, based on data from the RSV vaccine clinical development program. In further reports, the applicant is required to provide an adverse events table by age group (less than 65, between 65-74, 75-84 and 85 and above) and to discuss it.	REC	