EMA/CHMP/695763/2021
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005737/II/0033

Invented name: COVID-19 Vaccine Janssen

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

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

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	22 Nov 2021	22 Nov 2021
☐	CHMP Rapporteur Assessment Report	03 Dec 2021	04 Dec 2021
☐	CHMP members comments	07 Dec 2021	07 Dec 2021
☐	Updated CHMP Rapporteur Assessment Report	09 Dec 2021	11 Dec 2021
☒	Opinion	13 Dec 2021	14 Dec 2021

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 19 November 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to introduce an homologous booster dose (second dose) of COVID-19 vaccine Janssen based on interim efficacy, immunogenicity and safety results from different clinical studies including the two randomised, double blind, placebo-controlled Phase 3 studies COV3001 and COV3009. In addition, an update to introduce an heterologous booster dose of COVID-19 vaccine Janssen following completion of a primary vaccination with an approved mRNA COVID-19 vaccine is introduced based on immunogenicity and safety interim results from the phase 1/2 study DMID 21-0012. In addition, the MAH took the opportunity to update the efficacy data for the primary vaccination schedule based on final analysis from study COV3001. The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Introduction

COVID-19 Vaccine Janssen (also refer hereafter as Ad26.COV2.S) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The approved posology is a single dose of $5x10^{10}$ vp in 0.5 mL, to be administered intramuscularly.

In the current variation, the MAH is seeking a posology for homologous booster immunization at least 2 months after primary vaccination in individuals ≥18 years of age and the use of Ad26.COV2.S for heterologous booster immunization following completion of primary vaccination with an approved mRNA COVID-19 vaccine.

This assessment report (AR) summarises the available data on immunogenicity, efficacy and safety for participants in different studies who received a booster dose (second dose) of COVID-19 Vaccine Janssen at different time interval (2, 3, or 6 months) between the first and the second dose.

The durability of protection and of immunogenicity after a single dose of COVID-19 Vaccine Janssen is presented as data to support the need for a booster dose (second dose). Interim real-world-effectiveness (RWE) data from study COV4002 and a summary of additional RWE studies are also presented by the MAH.

The MAH also proposes the use of Ad26.COV2.S for heterologous booster immunization following completion of primary vaccination with an approved mRNA COVID-19 vaccine. Selected data from the 'Mix and Match study' (DMID 21-0012, published by Atmar et al.) are presented in support.

The Product Information has been updated accordingly.

3. Clinical Immunogenicity aspects

Results from several clinical studies were included to support the proposed homologous booster variation: the First-in-human trial COV1001, Phase 1 and 2 studies COV1002 and COV2001 and the Phase 3 trial COV3009. Data from the ongoing dedicated booster study COV2008 are not yet available. Study results from the Phase 1/2 study DMID 21-0012, were also included, to support the heterologous boost by COVID-19 Vaccine Janssen after a primary vaccination with an approved mRNA COVID-19 vaccine.

This section presents a summary of immunogenicity results from studies conducted by the MAH, focusing on the **durability of the immune response induced by primary vaccination with a single dose of Ad26.COV2.S** at the 5×10^{10} vp dose level and **homologous boostability** 2, 3 and 6 months after first vaccination (at 5×10^{10} vp or 1.25 $\times10^{10}$ vp dose levels).Most of the results described thereafter are for the original Victoria strain. Limited results are presented for the variants of concern (VOC).

Immunogenicity analyses were performed on the Per-protocol Immunogenicity (PPI) set, unless specified otherwise. The PPI is defined as all randomized and vaccinated participants for whom immunogenicity data are available, excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural SARS-CoV-2 infection occurring after screening (if applicable) are excluded from the analysis set, while samples obtained up to that point are included in the analysis.

For study COV3009, it should be noted that results are based on partial data as not all samples for the different timepoints have been analysed.

Due to a pause implemented across studies in the Ad26.COV2.S clinical development program in October 2020 upon a study pausing rule being met in study COV3001, blood draws for immunogenicity on the Day of second vaccination were delayed for the majority of COV1001 Cohort 3 participants from Day 57 onwards. For the majority of participants, the actual timing of Day 57 blood draws ranged from 86 to 107 days post vaccination (median visit = Day 87). Therefore, a sensitivity analysis (ie, only including participants with samples collected out of per protocol visit window) was performed on the Full Analysis Set (FAS) and the Day 239 timepoint (8 months), which is discussed in this document, is referred to as Day 268 (9 months).
The study pause delayed the second vaccination and blood draws for immunogenicity in COV1002 Cohort 1. The actual timing of the Day 57 blood draw ranged from 73 to 88 days postvaccination (median = 78 days) in Cohort 1. Therefore, data presented for Cohort 1 are added based on the sensitivity analysis and Day 57 timepoint is referred to as 'Day 78'.

No formal statistical testing of the immunogenicity data has been conducted. Descriptive statistics were calculated for continuous immunologic parameters at all timepoints.

Finally, data from the Phase 1/2 study DMID 21-0012, an ongoing heterologous platform boost study conducted by NIH/NIAID in the US (also referred to as Mix and Match study, published in Atmar *et al.* 2021) were also presented. This study is evaluating the immune responses in adult participants who received a **homologous or heterologous booster vaccination** at least 12 weeks after primary vaccination with an approved mRNA COVID-19 vaccine regimen (2 doses of Moderna-mRNA-1273 [100 µg] or 2 doses of Pfizer/BioNTech-BNT162b2 [30 µg]) or Ad26.COV2.S [1 dose 5×10^{10} vp].

3.1. Immunological assays

An overview of the immunological assays used in this document is provided in Table 1 and the definitions of responder rates and seropositivity of samples for these assays is presented in Table 2. Performance of the assays listed in *Table 1*were assessed at the time of initial conditional MA.

Table 1. Overview of development status of immunological assays use for analysis of immune responses in studies COV1001, COV1002, and COV2001

Assay	Analysis	Analyzing Lab	Phase 1/2a Assay Status	Phase 2/3 Assay Status
SARS-CoV-2 Spike (S) ELISA	Binding antibodies against SARS-CoV-2 Spike protein	Nexelis	Qualified	Validated
Wild-type SARS-CoV-2 VNA	Neutralizing antibodies against SARS-CoV-2	Public Health England	Qualified	Qualified
Ad26 VNA	Neutralizing antibodies against Ad26 vector backbone	Janssen	Qualified	Qualified
ADCP	Fc-mediated viral clearance	SeromYx	Qualified	Qualified

Table 2. Responder definitions for immunogenicity assays used

Assay	Sample Interpretation (Positive/Negative)	Responder Definition Post-vaccination Sample	
		Baseline Sample Negative	Baseline Sample Positive
SARS-CoV-2 Spike (S) ELISA	Positive if result >LLOQ	Responder if positive	Responder if ≥4-fold increase from baseline
SARS-CoV-2 VNA	Positive if result >LLOQ	Responder if positive	Responder if ≥4-fold increase from baseline
SARS-CoV-2 MSD	Positive if result >LOD	Responder if positive	Responder if ≥4-fold increase from baseline
Human SARS-CoV-2 Spike ADCP	Positive if result ≥LOD	Not applicable	Not applicable

ADCP: antibody-dependent cellular phagocytosis; ELISA: enzyme-linked immunosorbent assay; LOD: limit of detection; LLOQ: lower limit of quantification; VNA: wild-type virus neutralization assay (wild type or pseudovirus)

Additional assays were also used:

Flow cytometry - Intracellular staining (ICS)

ICS was used for the measurement of CD4+ Th1 and Th2 responses as well as of CD8+ T cell responses.
Please refer to conditional MA AR for further description of the assay.

Pseudotyped Virus Neutralization Assay (psVNA) - JBDA

A pseudotyped virus neutralization assay (psVNA) was performed by Janssen Bioassay Development and Automation (JBDA). Codon optimized, synthesized DNA encoding SARS-CoV-2 Spike protein (based on Wuhan-Hu-1; GenBank accession no. MN908947) C-terminally truncated by 19 amino acids was cloned into a derivative of the pCDNA3.1 expression vector (Thermo Fisher Scientific). Substitutions and deletions in the Spike protein gene open reading frame were introduced and confirmed using standard molecular biology techniques. HIV-based lentiviral pseudotyped particles harboring the SARS-CoV-2 Spike protein variants were produced using the ViraPower Lentiviral Expression system (Thermo

Fisher Scientific). As well as the original WA1/202 strain (with D614G mutation), pseudoviruses of the following variants were also generated: Beta (B.1.351 lineage), Gamma (P.1 lineage), Lambda (C.37 lineage) and Delta (B.1.617.2 lineage).

Serum standards, controls and serial diluted serum samples were incubated at room temperature with pseudovirus particles. After 1h incubation, the serum-particle mixture was inoculated onto Hek293T.ACE2.TMPRSS2 target cells which stably express the human ACE2 and human TMPRSS2 genes. Luciferase activity was measured 40h later, using NeoLite substrate (Perkin Elmer) and the EnSight Multimode Plate Reader (Perkin Elmer). SARS-CoV-2 neutralizing titers were calculated using a four-parameter curve fit as the sample dilution at which a 50% reduction (IC50) of luciferase readout was observed compared to the Control.

The assay was developed in-house at JBDA and is not qualified or validated.

Pseudotyped Virus Neutralization Assay (psVNA) - Monogram

Principle

A pseudotyped virus neutralization assay (psVNA) was partially validated and performed by Monogram. The measurement of neutralizing antibody activity was performed by generating HIV-1 pseudovirions that express the SARS CoV-2 spike protein from both the reference strain (with DG614G mutation) and the Beta variant (B.1.351 lineage). The pseudoviruses were prepared by co-transfecting HEK293 producer cells with an HIV-1 genomic vector and a SARS-CoV-2 envelope expression vector. Neutralizing antibody activity was measured by assessing the inhibition of luciferase activity in HEK293 target cells expressing the ACE2 receptor following pre-incubation of the pseudovirions with serially diluted serum samples. The expression of luciferase activity in target cells is inhibited by the presence of functional anti-SARS CoV-2 antibodies with neutralizing activity. Data were displayed by plotting the percent inhibition of luciferase activity vs. log10 reciprocal of the serum/plasma dilution and antibody titers are reported as the reciprocal of the serum dilution conferring 50% inhibition (IC50) of pseudovirus infection.

To ensure that the neutralizing activity measured was specific for SARS CoV-2, each test sample was also assessed using a non-specific pseudovirus (specificity control) that expresses a nonreactive envelope protein of one or more unrelated viruses (e.g. avian influenza virus).

Assay development and Qualification/validation

Assay Validation Reports were provided (Validation report for SARS-CoV-2 reference strain (D614G mutation): MG-SF-VALDVR1088.000, Validation report for SARS-CoV-2 Beta Variant: MG-SF-VALD-VR1095.000).

Repeatability testing was repeated based on six replicate determinations versus three replicate determinations as originally proposed. Assay repeatability was reassessed using alternative low titer samples to substitute for several initial low titer sample candidates that resulted titers below the assay MRD (<40). Assay linearity/dynamic range (LLOQ and ULOQ) was reassessed/extended by evaluating one or more additional high titer CoV-2 nAb sample candidates. The evaluation of assay repeatability based on ID80 titers was performed as amended for ID50 titers. Specific validation acceptance criteria were not applied to ID80 titer determinations. ID80 titers are considered validated if the evaluation of ID80 titers satisfies the established acceptance criteria for ID50 titers (CV$\leqslant$45%). The results of the PhenoSense SARS CoV-2 nAb is routinely reported as an ID50 titer and/or ID80 titer (1/Dilution). Results can be reported qualitatively (positive, negative) based on a pre-defined dilution cutoff (e.g., >50% inhibition at 1:40 dilution).

The PhenoSense SARS CoV-2 nAb Assay has been validated and qualified as an accurate method to quantitate anti-SARS CoV-2 nAb activity directed at the D614G Spike variant (Refer to the PhenoSense Anti-SARS CoV-2 Neutralizing Antibody Assay: D614G Variant Study (MG-SF-ST-ST0358)). Validation parameters and acceptance criteria were defined (p. 11 MG-SF-VALD-VR1088.000).

Results summary

Repeatability: Intra-assay variation of ID50 and ID80 titers is consistently <35% CV and averaged 19.8% for ID50 values and 15.0% for ID80 values.

Intermediate Precision: Total assay variation based on within-run and between-run components is <35% CV and averages ~20% for ID50 values and ~17% for ID80 values.

Linearity: ID50 and ID80 titer determinations exhibit a high degree of linearity across 2.5 log10 and 1.9 log10 ranges.

Limits of Quantitation: ID50 LLOQ= 42 and ULOQ= 9484; ID80 LLOQ= 84 and ULOQ= 3496. Extension of the ULOQ will be further assessed upon the identification of an appropriate high titer sample with the requisite volume for testing.

Report MG-SF-VALD-VR1095.000 describes a similar but partial validation of the assay for the beta variant (B.1.351), using n=6 unknown sera, n=12 B.1.351 sera, n=6 B.1.1.7 sera, n=6 P.1 sera, n=6 B.1.427/429 sera, and n=6 B.1.526 sera.

Partial validation and acceptance criteria were defined (p. 8 in MG-SF-VALD-VR1095.000). Within-run variation, assay repeatability, intermediate precision and linearity is acceptable. ID50 ULOQ= 25,529; LLOQ= 41.

Result expression and definition

Neutralizing antibody titers are expressed as IC50 units.

A participant was defined as a responder if they were negative at baseline (<LLOQ) and positive (>LLOQ) post vaccination OR were positive at baseline (>LLOQ) and showed an increase in titer from baseline of ≥4-fold.

Spike Protein Enzyme Linked Immunosorbent Assay (S-ELISA) - JBDA

IgG binding to SARS-CoV-2 spike (S) protein was measured by enzyme-linked immunosorbent assay (ELISA) using a recombinant and stabilized trimeric spike protein antigen based on the Wuhan-Hu-1 SARS-CoV-2 strain and the Beta and Delta variants. SARS-CoV-2 spike protein antigens (2.0µg/mL) were directly adsorbed on 96-well microplates for 2h at 37° C in a humidified incubator. Following incubation, plates were washed three times in PBS/0.05% Tween-20 (PBST), blocked with 1% Casein in PBS for 1h at room temperature and washed with PBS-T. Serum standards (high titer human convalescent and naïve reference sera), control antibodies, and serum samples were serial diluted (3-fold) before incubation on the plates for 1h at room temperature.

Plates were washed three times with PBS-T and incubated with peroxidase-conjugated Goat anti-Human IgG (Jackson Immuno Research) diluted in blocking buffer for 1h at room temperature. Plates were washed three times in PBS-T, and developed with detection substrate (Clarity Western ECL peroxide reagent and luminol enhancer, Bio-Rad) for 10 minutes at room temperature, protected from

light. The signal was read on an Envision plate reader (Perkin Elmer) as relative luminescence units (RLUs).

Titers are reported as log10 of EC50 (50% effective concentration), compared with a high titer serum sample used as an internal reference standard, with a lower limit of quantification at 1.218.

The assay was developed in-house at Janssen Bioassay Development and Automation and is not qualified or validated.

Neutralisation assay used in Heterologous booster study

Assay

The Duke NAb Laboratory for HIV and COVID-19 Vaccine Research and Development (Duke Nab Lab; PI: Dr. David Montefiori) assessed the magnitude, kinetics, duration, and breadth of SARS-CoV-2 neutralizing antibody responses in the DMID Protocol #21-0012 by using a fully validated assay in an environment that operates in compliance with Good Clinical Laboratory Practices (GCLP). Assays were performed on all samples with Spike-pseudotyped virus SARS-CoV-2 D614G. A subset of samples were assayed with Spike-pseudotyped virus SARS-CoV-2 B.1.617.2 AY.3 (Delta lineage variant) and with Spike-pseudotyped virus SARS-CoV-2 B.1.351 (Beta variant). These viruses were prepared by Dr. Montefiori's laboratory using a lentivirus for pseudotyping and a luciferase reporter gene for quantitative measurements of virus neutralization. Results are reported as Inhibitory Dilution 50 (ID50) and Inhibitory Dilution 80 (ID80) neutralization titers. These values represent the serum dilution that reduces relative luminescence units (RLU) by either 50% or 80% relative to the RLU in the virus control wells after subtraction of background RLU. This study was completed under the oversight of the Quality Assurance Unit for Duke Vaccine Immunogenicity Programs (QADVIP).

Neutralization of SARS-CoV-2 Spike-pseudotyped viruses was assessed in 293T/ACE2 cells as described in SOP "CFAR02-A0026 Measuring Neutralizing Antibodies Against SARS-CoV-2 Using Pseudotyped Virus and 293T/ACE2 Cells." This assay has been formally validated and is part of Drug Master File # 26862 with the Federal Drug Administration. Assay validation was performed with human serum samples and monoclonal antibodies using the D614G form of the Wuhan-1 Spike. This assay is in the process of being validated for B.1.351, but has not been validated using B.1.617.2. The assay is performed in 96-well flat-bottom clear standard non-coated or Poly-L-Lysine treated culture plates for high throughput capacity. Relative luminescence units are measured in 96-well flat bottom black/white plates for enhanced luminescence with minimal bleed-over. Use of a clonal cell line provided enhanced precision and uniformity.

SARS-CoV-2 Spike-pseudotyped viruses are prepared and titrated for infectivity by using mutated forms of an expression plasmid encoding codon-optimized full-length Spike of the Wuhan-1 strain (VRC7480) provided by Drs. Barney Graham and Kizzmekia Corbett at the Vaccine Research Center, National Institutes of Health (USA). Mutations were introduced into VRC7480 by site-directed mutagenesis using the QuikChange Lightning Site-Directed Mutagenesis Kit from Agilent Technologies. All mutations were confirmed by full-length Spike gene sequencing. The variants used are displayed in Table 3.

Table 3

Variant	Spike mutations
D614G	D614G
B.1.617.2 AY.3 (Delta)	T19R, G142D, Δ156-157, R158G, L452R, T478K, D614G, P681R, D950N
B.1.351 (Beta)	L18F, D80A, D215G, ΔL242-244, K417N, E484K, N501Y, D614G and A701V

Pseudovirions are produced in HEK 293T/17 cells by transfection using Fugene 6 Transfection Reagent and a combination of Spike plasmid, lentiviral backbone plasmid (pCMV ΔR8.2) and firefly Luc reporter gene plasmid (pHR' CMV Luc) in a 1:17:17 ratio in Opti-MEM (Life Technologies). Transfection mixtures are added to pre-seeded HEK 293T/17 cells in T-75/T-225 flasks containing growth medium and incubated for 16-20 hours at 37°C, followed by two additional days with fresh growth medium. Pseudovirions are titrated for infectious dose (TCID50) by making serial 3-fold or 5-fold dilutions in quadruplicate for a total of 11 dilutions in 96-well flat-bottom clear standard non-coated or poly-L-lysine-coated culture plates. An additional 4 wells serve as background controls; these wells received cells but no virus. Freshly suspended 293T/ACE2.MF cells are added (10,000 cells/well) and incubated for 66-72 hours. Medium is removed by gentle aspiration and 30 µl of Promega 1X lysis buffer added to all wells. After a 10 minute incubation at room temperature, 100-110 µl of Bright-Glo luciferase reagent is added to all wells, mixed, and 105 µl of the mixture added to a black/white plate (Perkin-Elmer). Luminescence is measured using a GloMax Navigator luminometer (Promega). TCID50 is calculated using the method of Reed and Muench.

Neutralization is measured by using lentiviral particles pseudotyped with SARS-CoV-2 Spike and containing a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). Luminescence is measured using a GloMax Navigator luminometer (Promega). Neutralization titers are the serum dilution at which RLUs are reduced by either 50% (ID50) or 80% (ID80) compared to virus control wells after subtraction of background RLUs. Serum samples are heat-inactivated for 30 minutes at 56°C prior to assay.

For assay internal quality controls (IQC), a qualified positive control is tested on each assay plate. The positive control used for assays with D614G is DH1043NHS, which consists of a potent RBD-specific neutralizing monoclonal antibody (mAb), DH1043, diluted in heat inactivated normal human serum (NHS) at 40 µg/ml. The positive control used for assays with B.1.617.2 and B.1.351 is DH1047NHS, which consists of a potent RBD-specific neutralizing mAb, DH1047, diluted in heat inactivated NHS at 100 µg/ml. Assay run controls consist of COVID-19 convalescent serum samples or SARSCoV-2 vaccine recipients with high, medium and low ID50 and ID80 titers against the test virus, plus a normal human serum negative control. In addition, internal quality control samples (IQC-High, IQC-Medium, and IQC-Low) from the IQC Program for SARS-CoV-2 Antibody Assay Monitoring (SAAM) program operated by the External Quality Assurance Program Oversight Laboratory (EQAPOL) were included in each experiment.

Reporting

The assay's lower limit of detection (LLOD) is 10. For descriptive analyses, values reported as below the LLOD are assigned a value of LLOD/2 = 5. Specific to Pseudovirus D614G, the lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) are as follows:

ID50	ID80
LLOQ = 18.5	LLOQ = 14.3
ULOQ = 45118	ULOQ = 10232

Levels that are reported as above the LLOD but below the Lower Limit of Quantification (LLOQ) are kept as reported. Values that are greater than the upper limit of quantification (ULOQ) are when actual values are provided. If actual values above the ULOQ are not provided, observations are replaced with a value equivalent to the ULOQ.

Selected summaries of neutralizing titers calibrated to the WHO standard International Units (IU50/mL and IU80/mL), are presented. Conversion was done using calibration factors specifically for the SARS-CoV- 2 D614G Pseudovirus: a factor of 0.242 for ID50 and a factor of 1.502 for ID80.

Binding Antibody assays used in Heterologous booster study

Binding Antibodies: 4-plex ECLIA V.2

Testing was performed using the automated 4-plex MSD method as detailed in in VRC-VIP SOP 5525: Multiplex (4-Plex) Assay for the detection of IgG antibodies against SARS-CoV-2 proteins in human sera. Quantification of IgG concentrations in serum/plasma were performed with a Beckman Biomek based automation platform. This variant 4-plex is in the final stages of validation of the S-2P-B.1.351 antigen and confirmation of validation of the S-2P-WA-1 antigen, all performed in alignment with the previously validated SARS-CoV-2 3-plex as well as the FDA provided guidance on variant validation (DMF 023422).

Briefly, MSD SECTOR® plates (384-well) are precoated by MSD with WA-1 SARS-CoV-2 spike (S- 2P), B.1.351 receptor binding domain (RBD) protein, Nucleocapsid (N) protein and B.1.351 spike protein in each well in a specific spot-designation for each antigen. The assay is to be performed with a Beckman Coulter Biomek based automation integration platform including the Biotek 405TS Plate Washer. Serum samples will be heat-inactivated for 30 minutes at 56oC prior to assay. Plates are blocked for 60 minutes at room temperature (RT) with MSD blocker A solution without shaking. Plates are washed and MSD reference standard (calibrator), QC test sample (pool of COVID-19 convalescent sera) and human serum test samples are added to the precoated wells in duplicates in an 8-point dilution series. Reference standard is added in triplicates. MSD Control sera (low, medium and high) are added undiluted in triplicates as per validated assay format. Additional assay controls might be added in triplicates. Samples are incubated at RT for 4 hours with shaking on a Titramax Plate shaker (Heidolph) at 1500 rpm. SARS-CoV-2 specific antibodies present in the sera or controls bind to the coated antigens. Plates are washed to remove unbound antibodies. Antibodies bound to the SARS-CoV-2 viral proteins are detected using an MSD SULFOTAGTM anti-human IgG detection antibody incubated for 60 minutes at RT and with shaking. Plates are washed and a read solution (MSD GOLDTM read buffer) containing electrochemiluminescence (ECL) substrate is applied to the wells, and the plate is entered into the MSD MESO Sector S 600 detection system. An electric current is applied to the plates and areas of well surface which form antigen-anti human IgG antibody SULFO-TAGTM complex will emit light in the presence of the ECL substrate.

The MSD MESO Sector S 600 detection system quantitates the amount of light emitted and reports the ECL unit response as a result for each test sample, control sample and reference standard of each plate. Analysis is performed with the MSD Discovery Workbench software, Version 4.0. Calculated ECLIA parameters to measure binding antibody activities will include interpolated concentrations or assigned arbitrary units (AU/mL) read from the standard curve. A 4-pl curve was used for the analysis. Data analysis was performed using Microsoft Excel and GraphPad Prism Version 8.0.

FFP 10-plex ECLIA

A fit-for-purpose (FFP) 10-plex ECLIA assay was developed and used to further assess IgG binding responses to various SARS-COV-2 spike variants of interest (VOIs) and VOCs antigens. Multiplexed Plates (MSD SECTOR® 96-well) precoated with up to ten antigens per panel are supplied by the manufacturer. Prior to any sample evaluation or data release, each 10-plex panel is functionally characterized and evaluated at the VIP, in addition to any quality control testing conducted by the manufacturer. On the day of the assay, the plate is blocked for 60 minutes with MSD Blocker A (5% BSA). The blocking solution is washed off and test samples are applied to the wells at 4 dilution (1:100, 1:500, 1:2500 and 1:10,000) unless otherwise specified and allowed to incubate with shaking for two hours. Plates are washed and Sulfo-tag labeled anti IgG antibody is applied to the wells and allowed to associate with complexed coated antigen – sample antibody within the assay wells. Plates are washed to remove unbound detection antibody. A read solution containing ECL substrate is applied

to the wells, and the plate is entered into the MSD Sector instrument. A current is applied to the plate and areas of well surface where sample antibody has complexed with coated antigen and labeled reporter will emit light in the presence of the ECL substrate. The MSD Sector instrument quantitates the amount of light emitted and reports this ECL unit response as a result for each sample and standard of the plate. Magnitude of ECL response is directly proportional to the extent of binding antibody in the test article. All calculations are performed within Excel and the GraphPad Prism software, version 7.0. Readouts are provided as Area Under Curve (AUC).

The method described has been previously published (A. Pegu et al.) , though the specific makeup of variant antigens included in 10-plex panels may vary. We note that only two of these VOC are reported here.

Reporting

For concentrations that are below the Lower Limit of Detection (LLOQ) numeric values equivalent to LLOQ/2 are assigned before and for all descriptive reporting. For concentrations greater than the upper limit of quantification (ULOQ) values are kept and reported when actual values are provided. If actual values above the ULOQ are not provided, observations are replaced with a value equivalent to the ULOQ. Bridging to the WHO standard Binding Antibody Units per milliliter (BAU/mL) was done using a conversion factor of 0.0090, specific to the IgG SARS-CoV-2 Spike antigen.

3.2. Participant information

A summary of participant disposition, study completion/withdrawal information, and baseline and demographic characteristics for studies COV1001, COV1002, COV2001, and COV3009 were provided.

Participant information for the studies COV1001 (Cohort 1a and Cohort 3), COV1002 and COV2001 were provided at initial conditional MA. For participant information for study COV3009, see efficacy section.

3.3. Results

3.3.1. Immunogenicity of Primary Single-dose Vaccination

3.3.1.1. Durability of the Single Dose Primary Vaccination Schedule - parental SARS-CoV-2 strain

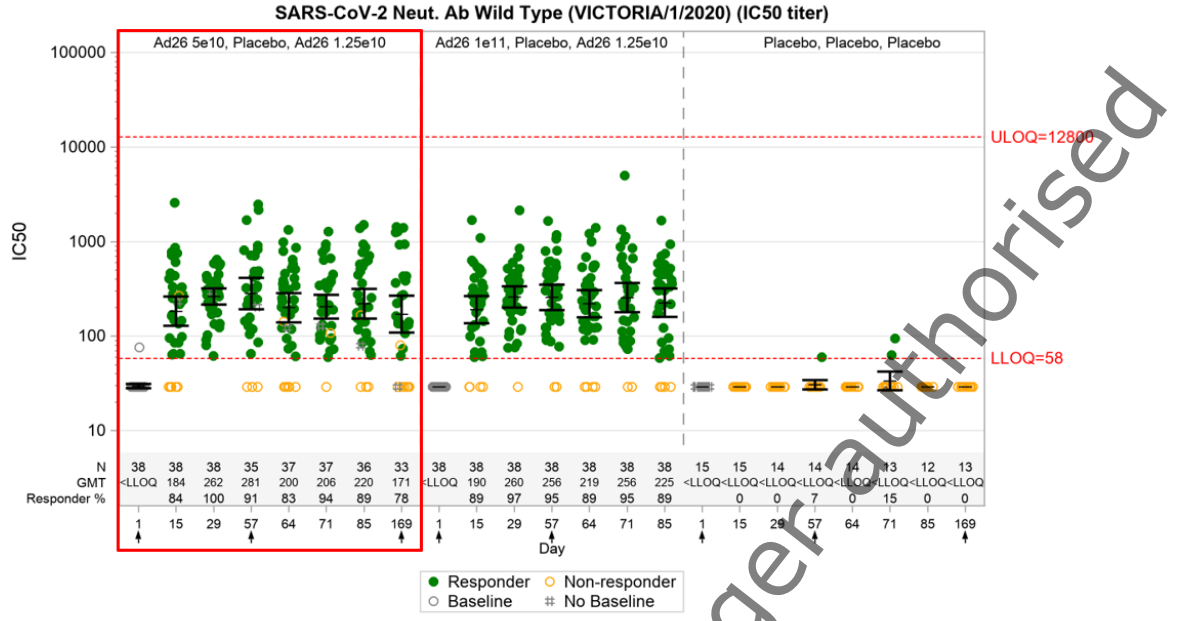
The main data on the durability of neutralizing and binding antibody responses against the original SARS-CoV-2 strain up to at least 6 months after the 1-dose primary vaccination schedule with Ad26.COV2.S ($5x10^{10}$ vp) are available from studies COV2001 (Group 5; up to 6 months [Day 169]) and COV1001 (Group 2 for both Cohort 1a and Cohort 3, up to 8-9 months [Day 239/Day 268]).

Study COV2001

In study COV2001, results for the nAb response (wtVNA) up to 6 months post-vaccination are available for 33 subjects, including 20 vaccinees of 18-55 yoa and 13 of ≥65 yoa. Binding Ab (S-ELISA, Nelexis) results are available for 73 subjects, including 44 vaccinees of 18-55 yoa and 29 of ≥65 yoa.

Graphical representations of neutralizing and binding antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in Figure 1 and Figure 2. Descriptive statistics

of neutralizing and of binding antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in Tables below.



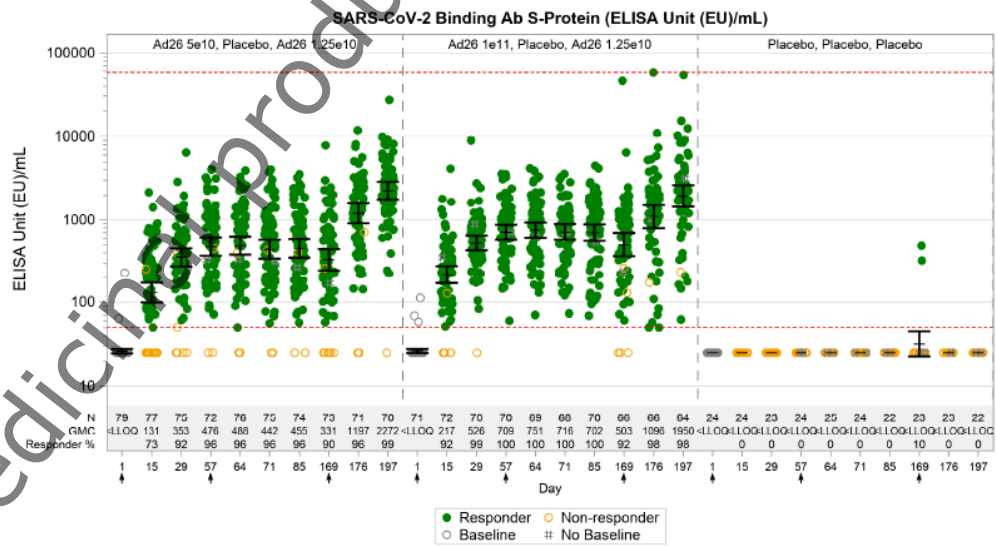
Note: Geometric mean titers with 95% CI shown in the figure.
Note: Ad26 5e10: Ad26.COV2.S 5x10 [10] vp; Ad26 1e11: Ad26.COV2.S 1x10 [11] vp.
The status of wtVNA assay is qualified. The assay range may change as the assay becomes validated.
Adapted from: [GIRHUM01-G456.RTF] [VAC31518\VAC31518COV2001\DBR_ADULT_IA2_SEQUESTERED\RE\PROD\GIRHUM01_456.SAS] 17AUG2021, 04:29

Figure 1. SARS-CoV-2 neutralization wtVNA-Victoria/1/2020 (IC50): Plot of the actual values over time; adult subjects, Group 456; PP immunogenicity set (study COV2001)

Table 4 SARS-CoV-2 neutralization wild type VNA - VICTORIA/1/2020 (IC50) for 18-55 years and ⩾65 years old subjects: Descriptive Statistics; Adult Subjects, Group 456; Per Protocol Immunogenicity Set (Study VAC31518COV2001)

	Ad26 5e10, placebo		**placebo, placebo**	
	18 - 55 years	**≥65 years**	**18 - 55 years**	**≥65 years**
analysis set: PP immuno	80	80	26	26
Baseline				
n	23	15	10	5
GMT (95% CI)	< LLOQ	< LLOQ (< LLOQ; < LLOQ)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	0	1 (6.7%) (0.2; 31.9)	0	0 (0.0; 52.2)
Day 15				
n	23	15	10	5
GMT (95% CI)	244 (158; 377)	119 (66; 217)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	22 (95.7%) (78.1; 99.9)	11 (73.3%) (44.9; 92.2)	0 (0.0; 30.8)	0 (0.0; 52.2)
responders n/N (%) (95% CI)	21/22 (95.5%) (77.2; 99.9)	10/15 (66.7%) (38.4; 88.2)	0/10 (0.0; 30.8)	0/5 (0.0; 52.2)
Day 29				
n	23	15	9	5
GMT (95% CI)	277 (211; 365)	240 (179; 322)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	23 (100.0%) (85.2; 100.0)	15 (100.0%) (78.2; 100.0)	0 (0.0; 33.6)	0 (0.0; 52.2)
responders n/N (%) (95% CI)	22/22 (100.0%) (84.6; 100.0	15/15 (100.0%) (78.2; 100.0)	0/9 (0.0; 33.6)	0/5 (0.0; 52.2)
Day 57				
n	21	14	9	5
GMT (95% CI)	281 (167; 472)	282 (147; 540)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ

positive sample (%) (95% CI)	19 (90.5%) (69.6; 98.8)	13 (92.9%) (66.1; 99.8)	1 (11.1%) (0.3; 48.2)	0 (0.0; 52.2)
responders n/N (%) (95% CI)	18/20 (90.0%) (68.3; 98.8)	13/14 (92.9%) (66.1; 99.8)	1/9 (11.1%) (0.3; 48.2)	0/5 (0.0; 52.2)
Day 64				
n	23	14	9	5
GMT (95% CI)	210 (130; 340)	185 (103; 334)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	20 (87.0%) (66.4; 97.2)	12 (85.7%) (57.2; 98.2)	0 (0.0; 33.6)	0 (0.0; 52.2)
responders n/N (%) (95% CI)	19/22 (86.4%) (65.1; 97.1)	11/14 (78.6%) (49.2; 95.3)	0/9 (0.0; 33.6)	0/5 (0.0; 52.2)
Day 71				
n	23	14	8	5
GMT (95% CI)	232 (161; 334)	169 (100; 283)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; 70)
positive sample (%) (95% CI)	23 (100.0%) (85.2; 100.0)	13 (92.9%) (66.1; 99.8)	1 (12.5%) (0.3; 52.7)	1 (20.0%) (0.5; 71.6)
responders n/N (%) (95% CI)	22/22 (100.0%) (84.6; 100.0)	12/14 (85.7%) (57.2; 98.2)	1/8 (12.5%) (0.3; 52.7)	1/5 (20.0%) (0.5; 71.6)
Day 85				
n	23	13	8	4
GMT (95% CI)	243 (151; 392)	186 (99; 349)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	22 (95.7%) (78.1; 99.9)	11 (84.6%) (54.6; 98.1)	0 (0.0; 36.9)	0 (0.0; 60.2)
responders n/N (%) (95% CI)	21/22 (95.5%) (77.2; 99.9)	10/13 (76.9%) (46.2; 95.0)	0/8 (0.0; 36.9)	0/4 (0.0; 60.2
Day 169				
n	20	13	8	5
GMT (95% CI)	200 (106; 378)	134 (68; 266)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	16 (80.0%) (56.3; 94.3)	10 (76.9%) (46.2; 95.0)	0 (0.0; 36.9)	0 (0.0; 52.2)
responders n/N (%) (95% CI)	16/19 (84.2%) (60.4; 96.6)	9/13 (69.2%) (38.6; 90.9)	0/8 (0.0; 36.9)	0/5 (0.0; 52.2)



Note: Geometric mean concentrations with 95% CI shown in the figure.
Note: Ad26 5e10: Ad26.COV2.S 5x10 [10] vp; Ad26 1e11: Ad26.COV2.S 1x10 [11] vp.
The status of the S ELISA assay is validated.

Figure 2. SARS-CoV-2 binding Ab (ELISA Unit [EU]/ml): Plot of the actual values over time; adult subjects, Group 456; PP immunogenicity set (study COV2001)

Table 5 SARS-CoV-2 S binding antibodies (ELISA Unit (EU)/mL): Descriptive Statistics; Adult Subjects, Group 456; Per Protocol Immunogenicity Set (Study VAC31518COV2001)

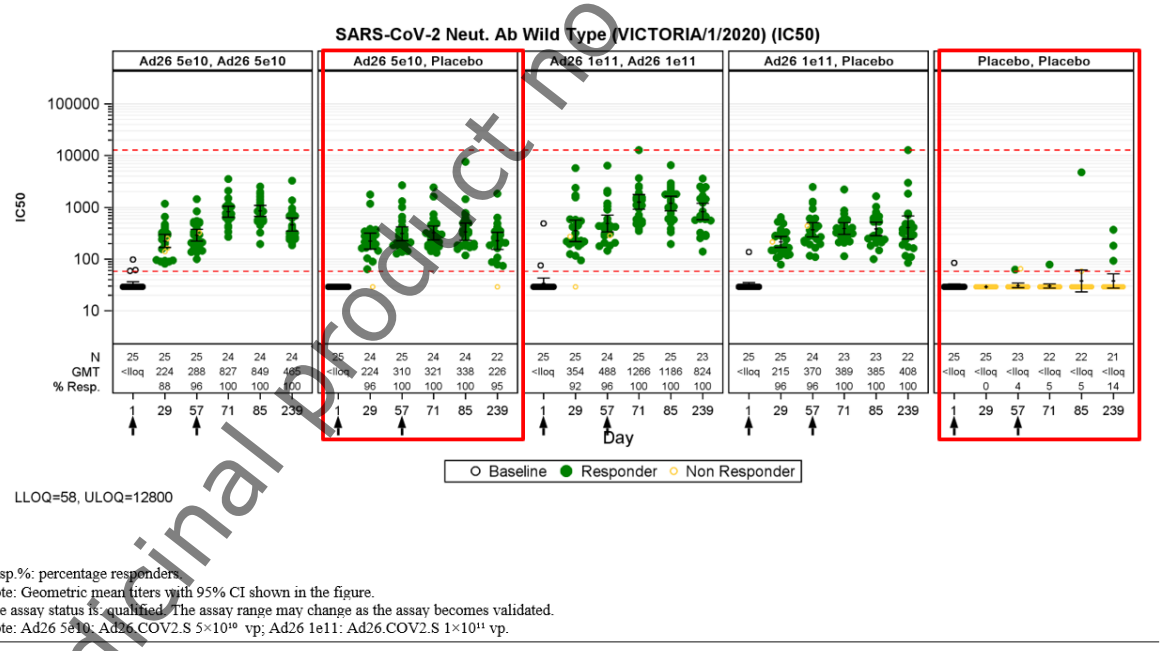
	Ad26 5e10, placebo		**placebo, placebo**	
	18 - 55 years	**≥65 years**	**18 - 55 years**	**≥65 years**
analysis set: PP immuno	80	80	26	26
Baseline				
n	49	30	14	10
GMT (95% CI)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ	< LLOQ	< LLOQ
positive sample (%) (95% CI)	1 (2.0%) (0.1; 10.9)	1 (3.3%) (0.1; 17.2)	0 (0.0; 23.2)	0 (0.0; 30.8)
Day 15				
n	48	29	14	10
GMT (95% CI)	191 (141; 260)	70 (< LLOQ; 112)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	43 (89.6%) (77.3; 96.5)	14 (48.3%) (29.4; 67.5)	0 (0.0; 23.2)	0 (0.0; 30.8)
responders n/N (%) (95% CI)	42/48 (87.5%) (74.8; 95.3)	14/29 (48.3%) (29.4; 67.5)	0/14 (0.0; 23.2)	0/10 (0.0; 30.8)
Day 29				
n	46	29	13	10
GMT (95% CI)	423 (320; 560)	265 (164; 430)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	45 (97.8%) (88.5; 99.9)	25 (86.2%) (68.3; 96.1)	0 (0.0; 24.7)	0 (0.0; 30.8)
responders n/N (%) (95% CI)	44/46 (95.7%) (85.2; 99.5)	25/29 (86.2%) (68.3; 96.1)	0/13 (0.0; 24.7)	0/10 (0.0; 30.8)
Day 57				
n	45	27	15	9
GMT (95% CI)	589 (435; 798)	334 (213; 525)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	44 (97.8%) (88.2; 99.9)	26 (96.3%) (81.0; 99.9)	0 (0.0; 21.8)	0 (0.0; 33.6)
responders n/N (%) (95% CI)	42/44 (95.5%) (84.5; 99.4)	26/27 (96.3%) (81.0; 99.9)	0/13 (0.0; 24.7)	0/9 (0.0; 33.6)
Day 64				
n	47	29	15	10
GMT (95% CI)	618 (456; 837)	333 (217; 510)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	46 (97.9%) (88.7; 99.9)	28 (96.6%) (82.2; 99.9)	0 (0.0; 21.8)	0 (0.0; 30.8)
responders n/N (%) (95% CI)	44/46 (95.7%) (85.2; 99.5)	28/29 (96.6%) (82.2; 99.9)	0/13 (0.0; 24.7)	0/10 (0.0; 30.8)
Day 71				
n	46	29	14	10
GMT (95% CI)	570 (419; 775)	296 (190; 461)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	45 (97.8%) (88.5; 99.9)	28 (96.6%) (82.2; 99.9)	0 (0.0; 23.2)	0 (0.0; 30.8)
responders n/N (%) (95% CI)	43/45 (95.6%) (84.9; 99.5)	28/29 (96.6%) (82.2; 99.9)	0/12 (0.0; 26.5)	0/10 (0.0; 30.8)
Day 85				
n	46	28	13	9
GMT (95% CI)	572 (420; 780)	313 (201; 486)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	45 (97.8%) (88.5; 99.9)	27 (96.4%) (81.7; 99.9)	0 (0.0; 24.7)	0 (0.0; 33.6)
responders n/N (%) (95% CI)	43/45 (95.6%) (84.9; 99.5)	27/28 (96.4%) (81.7; 99.9)	0/11 (0.0; 28.5)	0/9 (0.0; 33.6)
Day 169				
n	44	29	13	10
GMT (95% CI)	416 (294; 588)	234 (136; 403)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; 66)
positive sample (%) (95% CI)	42 (95.5%) (84.5; 99.4)	25 (86.2%) (68.3; 96.1)	1 (7.7%) (0.2; 36.0)	1 (10.0%) (0.3; 44.5)
responders n/N (%) (95% CI)	40/43 (93.0%) (80.9; 98.5)	25/29 (86.2%) (68.3; 96.1)	1/11 (9.1%) (0.2; 41.3)	1/10 (10.0%) (0.3; 44.5)
Day 176				

n	43	28	13	10
GMT (95% CI)	1719 (1321; 2236)	687 (404; 1168)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	43 (100.0%) (91.8; 100.0)	26 (92.9%) (76.5; 99.1)	0 (0.0; 24.7)	0 (0.0; 30.8)
responders n/N (%) (95% CI)	42/43 (97.7%) (87.7; 99.9	26/28 (92.9%) (76.5; 99.1)	0/11 (0.0; 28.5)	0/10 (0.0; 30.8)
Day 197				
n	41	29	13	9
GMT (95% CI)	2444 (1855; 3219)	2048 (1290; 3253)	< LLOQ	< LLOQ
positive sample (%) (95% CI)	41 (100.0%) (91.4; 100.0)	28 (96.6%) (82.2; 99.9)	0 (0.0; 24.7)	0 (0.0; 33.6)
responders n/N (%) (95% CI)	41/41 (100.0%) (91.4; 100.0)	28/29 (96.6%) (82.2; 99.9)	0/11 (0.0; 28.5)	0/9 (0.0; 33.6)

Study COV1001

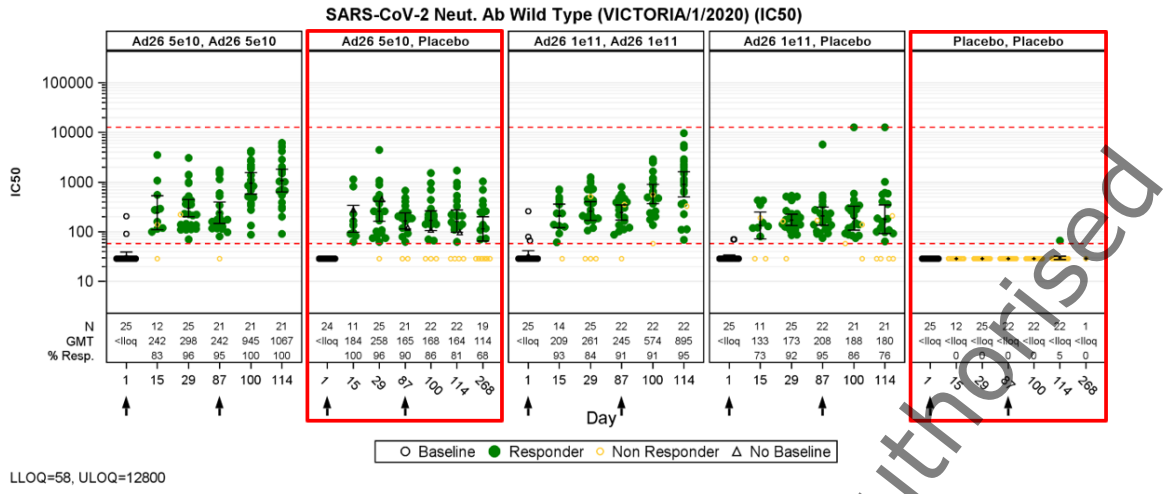
In study COV1001, results for the nAb response (wtVNA) are available for 22 vaccinees of 18-55 yoa (Cohort 1a, Group 2) and 19 vaccinees of ≥65 yoa (Cohort 3) up to 8 months following vaccination (Day 239). Results of binding Ab (S-ELISA) are available 68 vaccinees of 18-55 yoa and 67 of ≥65 yoa.

Graphical representations of neutralizing antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in Figures below.
Descriptive statistics of binding antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in Tables below.



Resp.%: percentage responders
Note: Geometric mean titers with 95% CI shown in the figure.
The assay status is: qualified. The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp.

Figure 3. SARS-CoV-2 neutralization wild type VNA-VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Cohort 1A; Per Protocol Immunogenicity Set (Study VAC31518COV1001)



The sensitivity analysis excludes the sentinel participants as of the time of second vaccination, so that the focus of the analysis is on the majority of the participants through time. Resp.%: percentage responders. Note: Geometric mean titers with 95% CI shown in the figure. The assay status is: qualified. The assay range may change as the assay becomes validated. This sensitivity analysis shows the second vaccination visit as Day 87, which was the median number of days post dose 1 that the second vaccination was received by the non-sentinel participants in Cohort 3. Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp.

Figure 4. SARS-CoV-2 wild type VNA - VICTORIA/1/2020: Plot of the Actual Values Over Time; Sensitivity Analysis; Cohort 3; FAS (VAC31518COV1001)

Table 6. SARS-CoV-2 binding antibodies S ELISA (ELISA Unit (EU)/mL): Descriptive Statistics; Cohort 1A; Per Protocol Immunogenicity Set (Study VAC31518COV1001)

	Ad26 5e10, placebo	**placebo, placebo**
	18 - 55 years	**18 - 55 years**
analysis set: PP immuno	75	76
Baseline		
n	75	76
GMT (95% CI)	<LLOQ (<LLOQ;<LLOQ)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	5(7%) (2%; 15%)	1(1%) (0%; 7%)
Day 29		
n	69	72
GMT (95% CI)	478 (379;603)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	69(100%) (95%; 100%)	2(3%) (0%; 10%)
responders n/N (%) (95% CI)	68/69(98.6%) (92.2%; 100.0%)	1/72(1.4%) (0.0%; 7.5%)
Day 57		
n	73	70
GMT (95% CI)	662 (518;844)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	73(100%) (95%; 100%)	3(4%) (1%; 12%)
responders n/N (%) (95% CI)	72/73(98.6%) (92.6%; 100.0%)	2/70(2.9%) (0.3%;9.9%)
Day 71		
n	67	65
GMT (95% CI)	612 (471;795)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	67(100%) (95%; 100%)	3(5%) (1%; 13%)
responders n/N (%) (95% CI)	67/67(100.0%) (94.6%;100%)	2/65(3.1%) (0.4%; 10.7%)
Day 85		
n	70	68

GMT (95% CI)	658 (502;862)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	70(100%) (95%; 100%)	5(7%) (2%; 16%)
responders n/N (%) (95% CI)	69/70(98.6%) (92.3%; 100.0%)	4/68(5.9%) (1.6%; 14.4%)
Day 239		
n	68	53
GMT (95% CI)	471 (345;642)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	68(100%) (95%; 100%)	4(8%) (2%; 18%)
responders n/N (%) (95% CI)	66/68(97.1%) (89.8%; 99.6%)	3/53(5.7%) (1.2%; 15.7%)

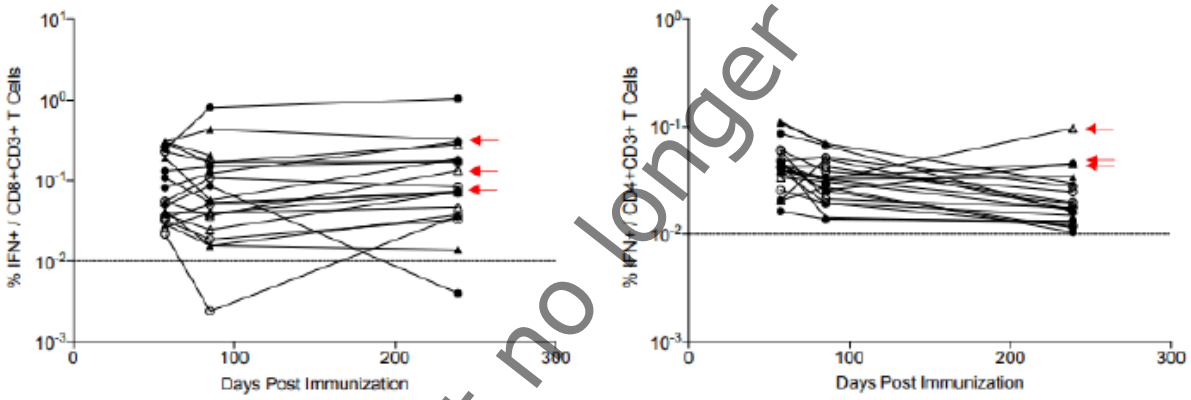
Table 7. SARS-CoV-2 binding antibodies S ELISA (ELISA Unit (EU)/mL): Descriptive Statistics; Sensitivity Analysis; Cohort 3; Full Analysis Set (Study VAC31518COV1001)

	Ad26 5e10, placebo	**placebo, placebo**
	≥65 years	**≥65 years**
analysis set: PP immuno	80	81
Baseline		
	79	80
GMT (95% CI)	<LLOQ (<LLOQ;<LLOQ)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	1(1%) (0%; 7%)	3(4%) (1%; 11%)
Day 15		
n	63	65
GMT (95% CI)	108 (81;145)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	46(73%) (60%; 83%)	4(6%) (2%; 15%)
responders n/N (%) (95% CI)	46/63(73.0%) (60.3%; 83.4%)	1/65(1.5%) (0.0%; 8.3%)
Day 29		
n	80	80
GMT (95% CI)	294 (238;364)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	78(98%) (91%; 100%)	2(3%) (0%; 9%)
responders n/N (%) (95% CI)	76/79(96.2%) (89.3%; 99.2%)	0/79(0.0%) (0.0%; 4.6%)
Day 87		
n	72	75
GMT (95% CI)	355 (280;450)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	70(97%) (90%; 100%)	4(5%) (1%; 13%)
responders n/N (%) (95% CI)	68/71(95.8%) (88.1%; 99.1%)	2/74(2.7%) (0.3%; 9.4%)
Day 100		
n	76	75
GMT (95% CI)	359 (282;457)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	74(97%) (91%; 100%)	3(4%) (1%; 11%)
responders n/N (%) (95% CI)	72/75(96.0%) (88.8%; 99.2%)	1/74(1.4%) (0.0%; 7.3%)
Day 114		
n	75	76
GMT (95% CI)	341 (266;437)	<LLOQ (<LLOQ;<LLOQ)
positive sample (%) (95% CI)	73(97%) (91%; 100%)	4(5%) (1%; 13%)

responders n/N (%) (95% CI)	72/74(97.3%) (90.6%; 99.7%)	2/75(2.7%) (0.3%; 9.3%)
Day 268		
n	67	10
GMT (95% CI)	375 (235;597)	91 (<LLOQ;637)
positive sample (%) (95% CI)	59(88%) (78%; 95%)	2(20%) (3%; 56%)
responders n/N (%) (95% CI)	58/66(87.9%) (77.5%; 94.6%)	2/10(20.0%) (2.5%; 55.6%)

Of note, as part the COV1001 study, 25 participants (18 to 55 years of age) at a single clinical site were enrolled to assess the immunogenicity of the Ad26.COV2.S vaccine in depth (COV1001 Cohort 1b). Overall, COV1001 Cohort 1b data confirm that Ad26.COV2.S elicited durable humoral and cellular immune responses for at least 8 months following vaccination in this age group. The observed humoral response was in line with the results of Cohort 1a.

The durability of the cellular immune response was also assessed in this cohort. The subject that received 1 single dose at the approved dose level are represented by the filled triangles (Figure 5).



Filled circles=1×10^{11} vp, PL; open circles= 1×10^{11} vp, 1×10^{11} vp; filled triangles= 5×10^{10} vp, PL; open triangles= 5×10^{10}, 5×10^{10} vp. Dotted lines show LLOQ. Note: red arrows highlight three individuals who developed breakthrough SARS-CoV-2 infection (filled circle; N=1) or who received mRNA vaccines (open triangles; N=2) between Day 71 and Day 239.

Figure 5. Participant Profiles of SARS-CoV-2 WA1/2020 CD4+ and CD8+ T-cell Responses (ICS) After Ad26.COV2.S Vaccination, Cohort 1b (VAC31518COV1001)

3.3.1.2. Immunogenicity of Primary Single-dose Vaccination against VOCs

Neutralizing antibodies against SARS-CoV-2 VOC, ie, B.1.1.7 (VUI2020 12/01, Alpha, Kent), B.1.351 (20H/501Y.V2, Beta, Republic of South Africa [RSA]), and B.1.617.2 (Delta) after 1 dose of Ad26.COV2.S at the of 5×10^{10} vp level, were measured in selected samples from COV1001 Cohort 1a. 6 paired samples of vaccinees having received 1 single dose of the vaccine at the approved dose level were tested for the Alpha and Beta strains at Day 29 and Day 71 following vaccination. For the Delta variant, the 6 samples were also tested at Day 239 in addition to both earlier timepoints. Immunogenicity against VOCs (alpha, kappa, delta, gamma, epsilon, beta) was also assessed over time in subjects from Cohort 1b. Overall data indicate a higher immune response against the original strain, and lower immune responses against the Beta and Delta strains, with a trend to increase from Day 29 to Day 71. nAb against the Delta variant could still be detectable at Day 239 post-vaccination, but not in all samples.

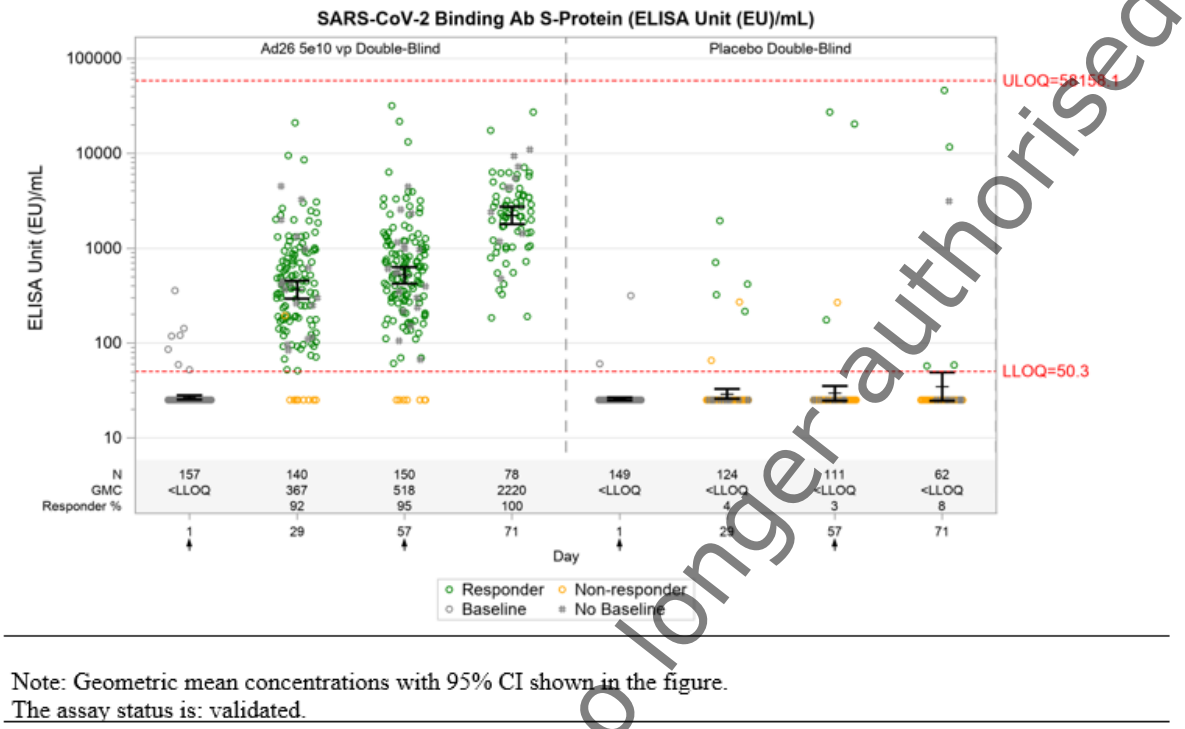
3.3.2. Immunogenicity after booster (second dose) vaccination

3.3.2.1. Homologous Booster Vaccination 2 to 3 Months After Dose 1 (5×10^{10} vp, 5×10^{10} vp Dose Level) - parental SARS-CoV-2 strain

3.3.2.1.1. Study COV3009 – Booster dose (second dose) at 2 Months

In study COV3009, immunogenicity of a booster dose (second dose) administered 2 months after the first vaccination was evaluated in healthy adults aged ≥18 years of age, including older adults aged ≥60 years of age. Participants received Ad26.COV2.S at the selected dose level of $5x10^{10}$ vp as the first dose and received Ad26.COV2.S at a dose level of $5x10^{10}$ vp as the booster dose (second dose), 2 months (Day 57) after the first vaccination. Immunogenicity data of study COV3009 are available for a limited number of subjects of the immunogenicity subset and only up to 14 days post-second vaccine dose (i.e. Day 71).
Results are presented overall (total of 157 vaccinated subjects) and by subgroups (age, comorbidities). Baseline results are available for 37 and 36 vaccinated subjects of 18-59 yoa, without and with comorbidities respectively, and for 45 and 36 vaccinated subjects ≥60 yoa, without and with comorbidities respectively. The number of subjects included in the Day 71 analyses are even lower: 17 and 15 vaccinated subjects of 18-59 yoa, without and with comorbidities respectively, and for 24 and 22 vaccinated subjects ≥60 yoa, without and with comorbidities respectively.
Ab GMT increases from baseline up to 2 months post-dose one (baseline GMT [95% CI]: < LLOQ [< LLOQ; < LLOQ]; Day 29 GMT [95% CI]: 367 [295; 456]; Day 57 GMT [95% CI]: 518 [422; 635]). These results are consistent with those observed for Group 5 of study COV2001 (both 18-55 yoa and ≥65 yoa) and Group 2 of Cohort 1a of study COV1001 (18-55 yoa). The second vaccine dose increased the GMT up to 2220 (95% CI: 1794; 2748). The GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination is thus 4.7 (3.8-5.7).
Responder rates were high pre- (Day 57 % responders [95% CI]: 94.7 [89.4; 97.8]) and post- (Day 71 % responders [95% CI]: 100.0% [94.7; 100.0]) booster dose (second dose). Both GMTs and responder rates were low in the placebo group at each timepoint.
If the results are analyzed by age and the presence of comorbidities, some differences in vaccine responses are observed between subgroups.
Older adult individuals (both without and with comorbidities) tend to have a lower level of Ab 1 month post-vaccination (Day 29-GMT [95% CI] of 318 [222; 455] and of 287 [169; 490] in older adults without and with comorbidities, respectively) when compared to the younger adults (Day 29-GMT [95% CI] of 493 [328; 742] and of 419 [252; 695] in younger adults without and with comorbidities, respectively). However, this difference is not observed anymore before the boost (Day 57) for both older adult subgroups (Day 57-GMT [95% CI] of 465 [342; 632] and of 423 [268; 667] in older adults without and with comorbidities, respectively) and young adult subjects with comorbidities (Day 57-GMT [95% CI] of 479 [293; 784]). Young individuals without comorbidities tend to have a higher level of S-specific Ab Day 57 (GMT [95% CI] of 760 [491; 1178]).
Young individuals without comorbidities also tend to have a higher level of S-specific Ab following the second vaccine dose (GMT [95% CI] of 3664 [2734; 4910]) when compared to the young adult subjects with comorbidities (GMT [95% CI] of 1804 [948; 3431]) and to both groups of older adult subjects (GMT [95% CI] of 2161 [1533; 3048] and of 1790 [1118; 2864] in older adults without and with comorbidities, respectively). A similar trend for lower Ab titer in the older adult subjects with and without comorbidities compared to both groups of younger adult subjects is observed post-boost.
Consistent with the lower GMTs at 1 month post-dose 1 observed in the older adult subjects, responder rates were also lower when compared to the younger adult subjects at Day 29 (responder rate [95% CI] of 100.0% [87.2; 100.0] and of 93.3% [77.9; 99.2] in younger adults without and with

comorbidities, respectively, and of 89.2% [74.6; 97.0] and of 86.2% [68.3; 96.1] in older adults without and with comorbidities, respectively). Responder rates were high pre- and post-boost in all 4 subgroups (at least 90% pre-boost and 100% post-boost).
Spike-specific binding antibody concentrations and responder rates are provided below.



Note: Geometric mean concentrations with 95% CI shown in the figure.
The assay status is: validated.

Figure 6. SARS-CoV-2 binding Ab (ELISA Unit [EU/ml]): Plot of the actual values over time ; adult subjects; PP immunogenicity set (study COV3009)

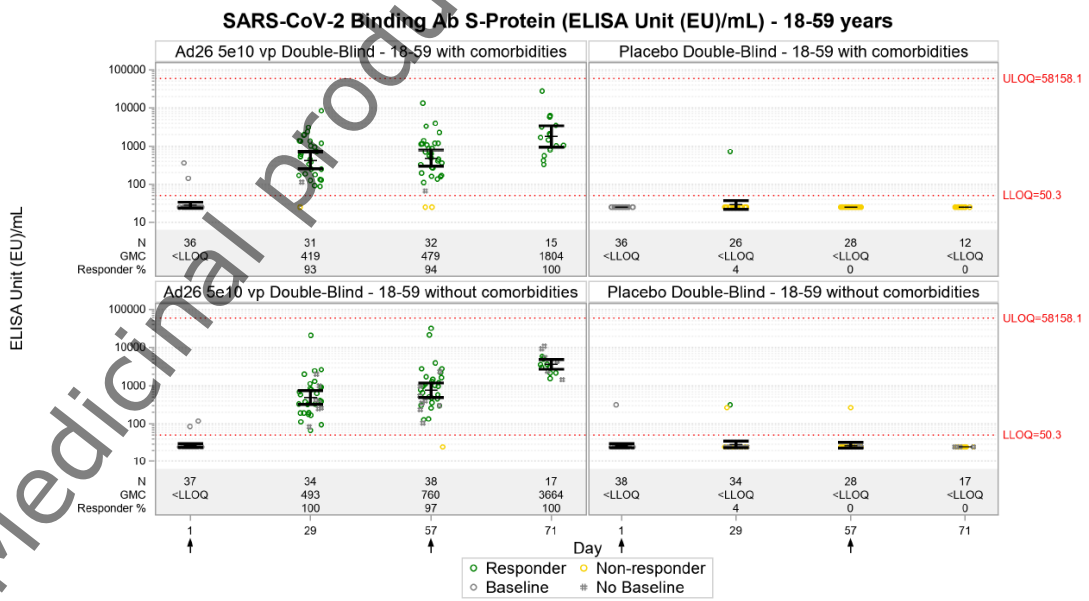


Figure 7. SARS-CoV-2 binding Ab (ELISA Unit [EU/ml]) by age and comorbidity strata: Plot of the actual values over time ; adult subjects, 18-59 yoa; PP immunogenicity set (study COV3009)

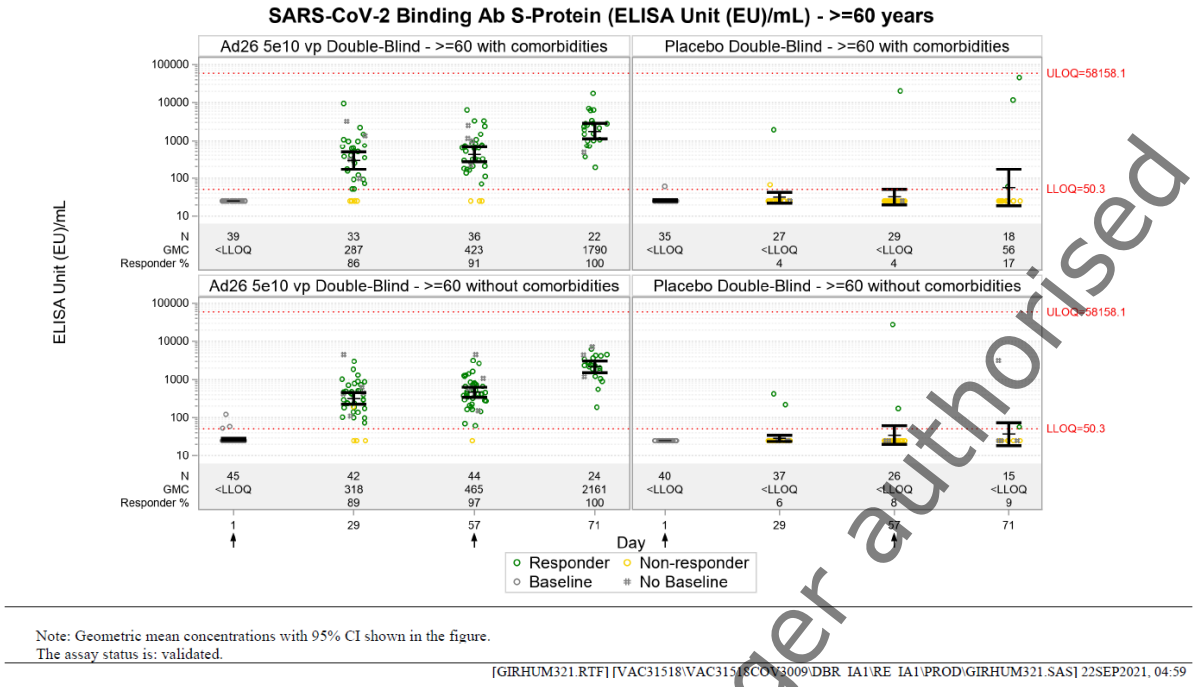


Figure 8. SARS-CoV-2 binding Ab (ELISA Unit [EU/ml]) by age and comorbidity strata: Plot of the actual values over time ; adult subjects, ≥60 yoa; PP immunogenicity set (study COV3009)

3.3.2.1.2. Study COV2001 – Booster dose (second dose) at 2 or 3 months

Participants >18 years of age received a booster dose (second dose) of Ad26.COV2.S (5×10^{10} vp) either at Day 57 (2 months; Group 1) or at Day 85 (3 months; Group 9). Graphical representations of neutralizing antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in Figure 9.

Immunogenicity data following the administration of a booster dose (second dose) of the vaccine, at a dose level of 5×1010 vp, are available for 75 and 127 subjects of study COV2001 for nAb and binding Ab, respectively.

- Among the 75 participants for whom nAb data are available up to 1 month post-dose 2, 38 received the second vaccine dose 56 days after the first one (group 1), and 37 received the booster dose (second dose) 84 days after the first dose (group 9).
  Among the subjects that received the 2 vaccine doses at 2 months interval (group 1), 23 were 18-55 yoa and 15 were ⩾65 yoa.
  Among the subjects that received the 2 vaccine doses at 3 months interval (group 9), 22 were 18-55 yoa and 15 were ⩾65 yoa.
- Among the 127 participants for whom binding Ab data are available up to 1 month post-dose 2, 80 received the second vaccine dose 56 days after the first one (group 1), and 47 received it 84 days after the first dose (group 9).
- Among the 80 subjects that received the 2 vaccine doses at 2 months interval (group 1), 52 were 18-55 yoa and 28 were ⩾65 yoa. Binding Ab results at Day 169 post-dose 1 were also available for 50 and 27 younger adult and older adult subjects, respectively.
- Among the 47 subjects that received the 2 vaccine doses at 3 months interval (group 9), 27 were 18-55 yoa and 20 were ⩾65 yoa.

The **booster dose** (**second dose) given 2 months after the first dose administration** (Day 57) induces an increase in nAb titer up to Day 71, followed by a slight decrease that can be observed at

Day 85 (1 month post-dose 2); GMT (95% CI) increased from 212 (142-314) at Day 57 to 518 (354-758) at Day 71 and, then slightly decreased to 424 (301-597) at Day 85. The GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination is thus 1.8 (1.4-2.4).

The same pattern of responses is overall observed for the binding antibodies. GMT (95% CI) increased from 425 (334-541) at Day 57 to 1745 (1415-2151) at Day 71, and slightly decreased to 1655 (1335-2052) at Day 85 when the second vaccine dose is administered 2 months after the first one.

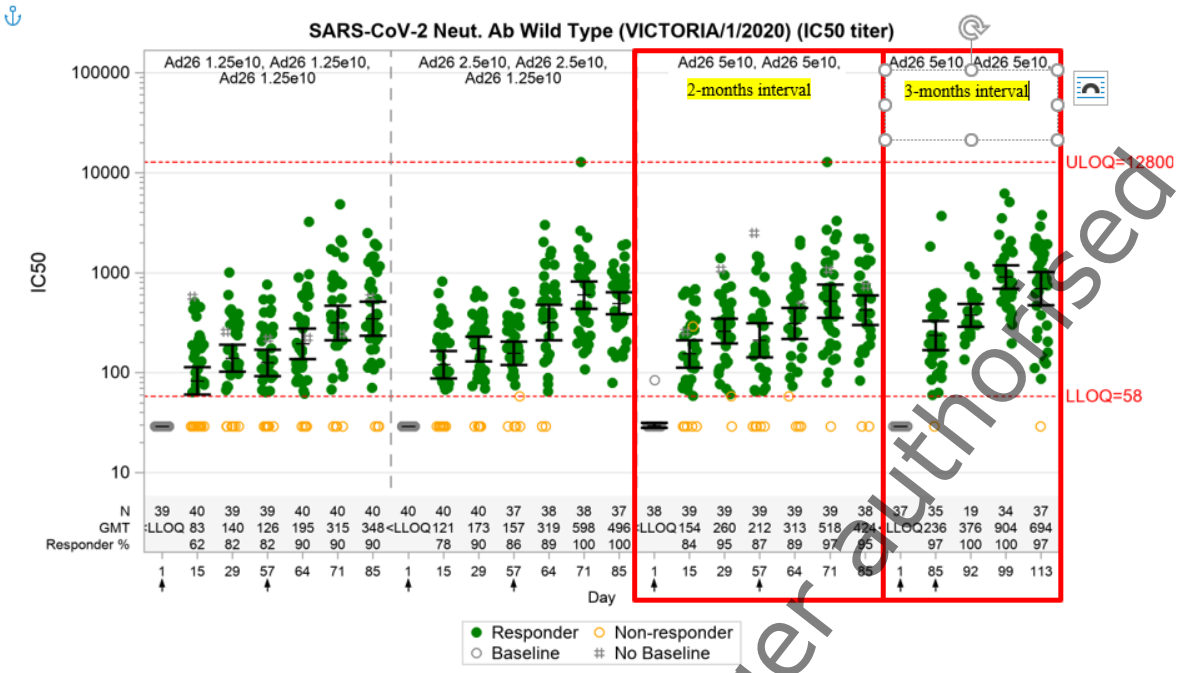
Similarly, the **booster dose (second dose) given 3 months following the first dose administration** (Day 85) induces an increase in nAb titer up to Day 99, followed by a slight decrease observed at Day 113 (1 month post-dose 2); GMT (95% CI) increased from 236 (169-328) at Day 85 to 904 (691-1184) at Day 99 and, then slightly decreased to 694 (473-1018) at Day 113. The GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination is thus 2.9 (2.0-4.3).

When the booster dose (second dose) is given 3 months after the first dose administration, GMT (95% CI) increased from 421 (310-571) at Day 85 to 2826 (2065-3870) at Day 99 and then decreased to reach 2466 (1876-3241) at Day 113.

The differences in nAb and binding Ab levels observed between both groups is less marked at 1 month post-dose 2 than at 14 days post-dose 2. Whether a difference will still be observed at later timepoints post-dose 2 is currently not known.

For group 1, who have an interval of 2 months between primary and booster vaccination, nAb titers are in line with the observations for binding Abs. GMT for the older adult participants tends to be lower than for the younger adult subjects pre-dose 2 (Day 57-GMTs [95% CI] of 169 [80; 357] and of 243 [150; 394] for the older and younger adult subjects, respectively). At one month post-dose 2 (Day 85), nAb GMTs (95% CI) increased to 346 (158; 756) and 477 (338; 674), in the older and younger adults, respectively.

Also for group 9, who have an interval of 3 months between primary and booster vaccination, nAb titers are in line with the observations for binding Ab. Pre-dose 2 (Day 85) GMTs (95% CI) are similar between older and younger adults (215 [115; 401] and 250 [166;378], for older and younger adults, respectively). However, 1 month post-dose 2 (Day 113), nAb GMTs are higher for the older adults compared to the younger (875 [477;1606] and 593 [351; 1001], for older and younger adults, respectively. Of note, CIs were large.



Note: Geometric mean titers with 95% CI shown in the figure.
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.
The status of wtVNA assay is qualified. The assay range may change as the assay becomes validated.

Figure 9. SARS-CoV-2 neutralization wtVNA - Victoria/1/2020 (IC50): Plot of the actual values over time ; adult subjects, group 1239 ; PP immunogenicity set (study COV2001)

3.3.2.1.3. Study COV1001 –Booster dose (second dose) at 2 or 3 months

Cohort 1a (18 to 55 years of age) and Cohort 3 (≥65 years of age) Group 1 participants received a booster dose (second dose) of Ad26.COV2.S ($5x10^{10}$ vp) at Day 57 (2 months; Cohort 1a) or at Day 87 (3 months; Cohort 3).

Humoral responses following a second vaccine dose - Neutralizing and Binding Antibody Responses

nAb results post-booster dose (second dose) for 24 participants of Cohort 1a and 21 participants of Cohort 3 are available. Binding Ab results post-booster dose (second dose) for 70 participants of Cohort 1a and 71 participants of Cohort 3 are available.

Graphical representations of neutralizing antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in the Figures below.

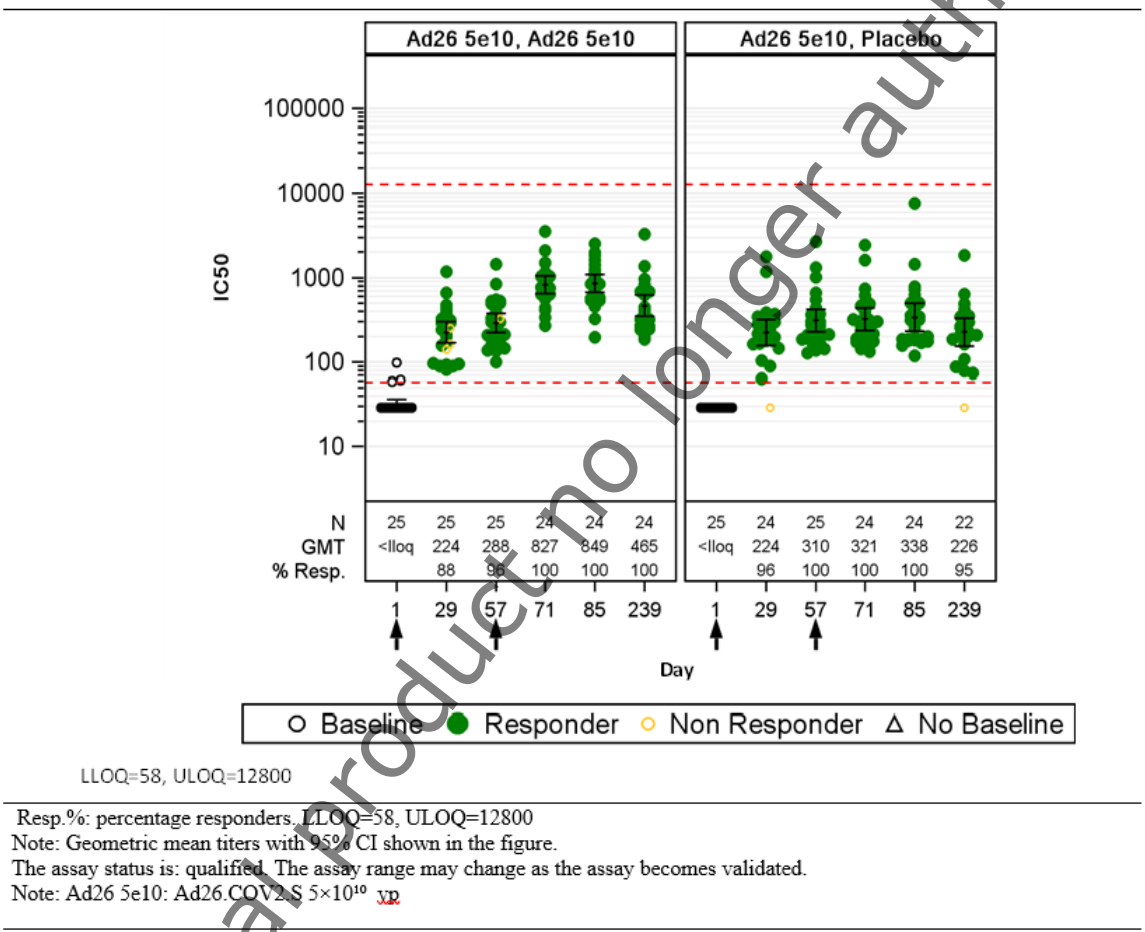
Because of the different time interval between vaccine doses applied for the younger adult and the older adult participants, results cannot be compared between both cohorts.

18-55 yoa adults (Cohort 1a)

The booster dose (second dose) given at 2 months following the first dose administration (Day 57) induces an increase in nAb titer that is maintained up to Day 85 (1 month Post-dose 2). The GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination is thus 2.9 (2.1-3.8). At Day 239, a decrease of nAb titer is observed. nAb GMTs (95% CI) decreased from 849 (664-1086) at Day 85 to

465 (348-620) at Day 239. Ab level were not measured between Day 85 and Day 239. It is thus not known when the decrease starts. Day 239-GMT is higher than the value observed at 1 month post-first dose (Day 29-GMT, 95% CI: 224, 168-298). Of note, the same pattern of response is observed for the higher dose level.

Similarly than observed for nAb, the level of binding Ab was increased 14 days following the second vaccine dose and maintained up to Day 85 (1 month Post-dose 2) (Day 85-GMT, 95% CI: 1994, 1674-2375; GMT, 95% CI fold-increase from pre-dose 2 to 1 month post-vaccination: 2.5, 2.1-3.1) before to decline to a GMT value of (95% CI) 933 (752-1159) at Day 239.



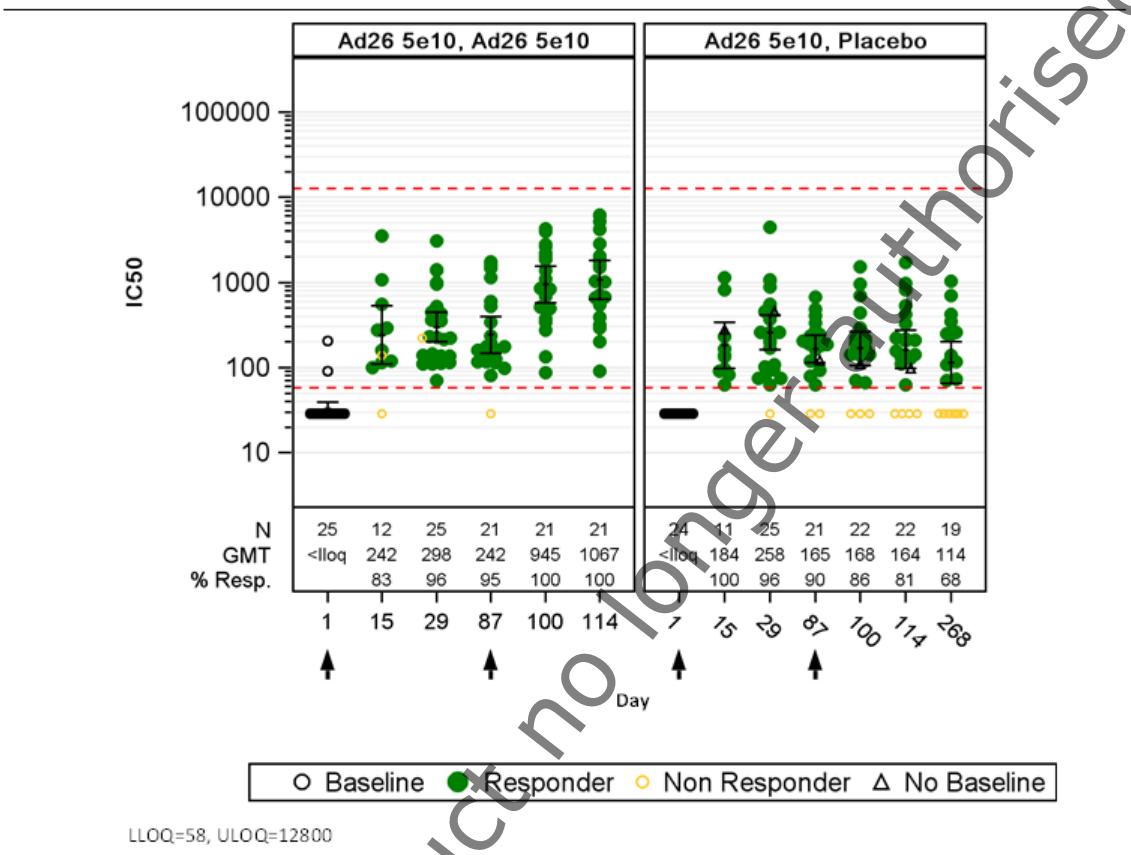
Resp.%: percentage responders, LLOQ=58, ULOQ=12800
Note: Geometric mean titers with 95% CI shown in the figure.
The assay status is: qualified. The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp

Figure 10. SARS-CoV-2 neutralization wtVNA - Victoria/1/2020 (IC50): Plot of the actual values over time ; Cohort 1a (18-55 yoa); PP immunogenicity set (study COV1001)

≥65 yoa adults (Cohort 3)

The booster dose (second dose) was given 3 months following the first dose administration (because of study pause in study COV3001) and induced an increase in nAb titer that is maintained up to 1 month post-dose 2 (Day 29-GMT, 95% CI: 298, 200-444 versus Day 114-GMT, 95% CI: 1067, 630-1807). The GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination is thus 4.3 (3.1-5.8). There are no longer term data.

Similarly than observed in the younger adults, the level of binding Ab was increased 14 days following the booster dose (second dose) and maintained up to Day 114 (1 month Post-dose 2) (Day 114-GMT, 95% CI: 2040, 1603-2595; GMT, 95% CI fold-increase from pre-dose 2 to 1 month post-vaccination: 4.5, 3.6-5.7) before to decline to a GMT value of (95% CI) 1099 (765-1581) at Day 268. The Ab level is higher than 1 month post-dose 1, i.e. GMT (95% CI) of 317 (250-403).



The sensitivity analysis excludes the sentinel participants as of the time of second vaccination, so that the focus of the analysis is on the majority of the participants through time.
Resp.%: percentage responders. Note: Geometric mean titers with 95% CI shown in the figure.
The assay status is: qualified. The assay range may change as the assay becomes validated. This sensitivity analysis shows the second vaccination visit as Day 87, which was the median number of days post-dose 1 that the second vaccination was received by the non-sentinel participants in Cohort 3.
Note: Ad26.5e10: Ad26.COV2.S 5×10^{10} vp

Adapted from: girhum61_sa1-c3.rtf] [Findings/is/pgm/is21.sas] 25AUG2021, 5:42:25PM SAS 9.4

Figure 11. SARS-CoV-2 neutralization wtVNA - Victoria/1/2020 (IC50): Plot of the actual values over time; sensitivity analysis; Cohort 3 (≥65 yoa); FAS (study COV1001)

Humoral responses - Functional Antibody Characterization

In study COV1001 (Cohorts 1a, 1b, and 3), antibody-dependent cellular phagocytosis of SARS-CoV-2 trimeric Spike antigen was measured by an ADCP assay.

Results post-booster dose (second dose) were obtained for 72 and 73 participants of Cohorts 1a and 3, respectively, that were vaccinated with 2 vaccine doses, at a dose level of 5x1010 vp, given at 2 (Cohort 1a) of 3 (Cohort 3) months interval.

The proportion of positive samples post-dose 2 tend to increase from pre- to post-dose 2 in both cohorts. The same trend was observed for the Phagocytic score GMs. In the younger adult subjects (Cohort 1a), the Phagocytic score GMs (95% CI) increased from 29 (23-36) at Day 57 to 71 (60-83) at Day 71 and 87 (75-100) at Day 85. In the older adult subjects (Cohort 3), the GMs (95% CI) increased from 26 (21-33) at Day 87 to 77 (63-94) at Day 100 and 89 (73-108) at Day 114.

Data from Cohort 1b are too limited (and mixed with the other regimen tested in the study) to be interpreted.

Cellular immunity

PBMCs were collected from 39 participants of group 2 of Cohort 1a (18-55 yoa adults,) and of 40 participants of group 1 of Cohort 3 (≥65 yoa adults).

CD4 Th1 cells were defined as CD4+ T cells expressing IFNγ and/or IL-2 (Th1), but not Th2 cytokines, and CD8 Th1 cells were defined as CD8+ T cells expressing IFNγ and/or IL-2.

Following the second vaccine dose in younger adults, the proportion of subjects with S-specific CD4+ Th1 response were not increased. In addition, no increase in median response of the positive samples was observed. Similar observations were made for the CD8 T cell response.

A slight increase of the proportion of positive subjects with detectable S-specific CD4+ Th1 response was observed after the booster dose (second dose) in the older adult group (% positive sample [95% CI] of 47% [30%-65%] at Day 57 versus 66% [49%-80%] at Day 71), but with 95% CIs overlapping. No increase in the median response of the positive samples was observed following the second vaccine dose for this group.

Similarly, a slight increase in the proportion of positive subjects with detectable S-specific CD8+ T cells was observed following the booster dose (second dose) in the older adult group (% positive sample [95% CI] of 56% [38%-73%) at Day 57 versus 64% [46%-79%] at Day 71), but with 95% CIs overlapping. However, no trend for an increase of the median response of S-specific CD8+ T cells was observed in the positive samples for this group.

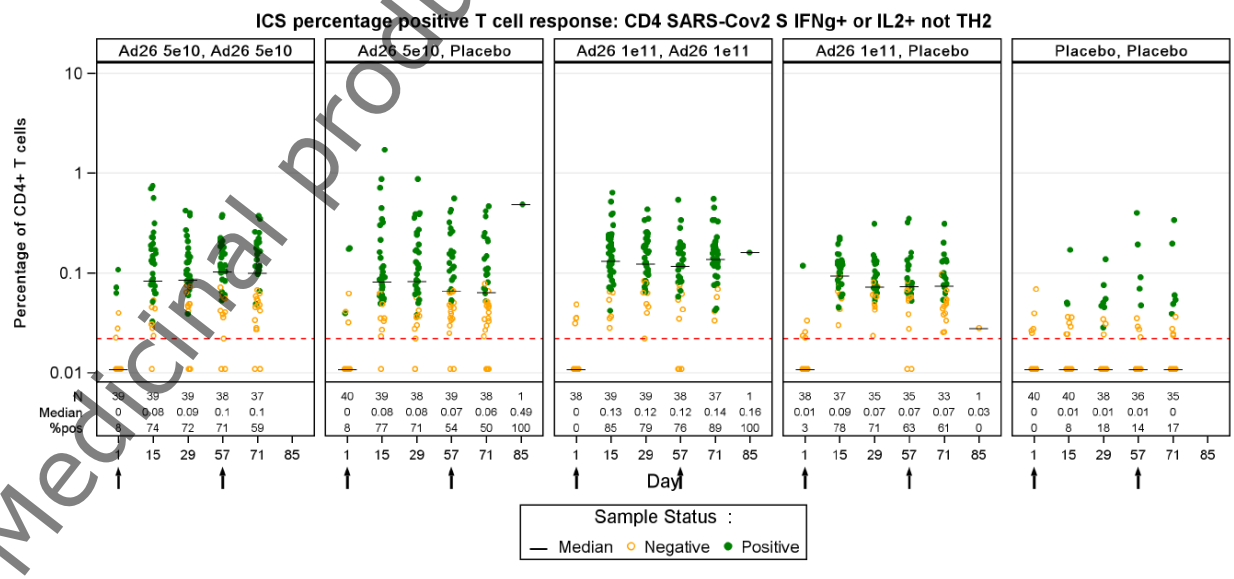


Figure 12. Cytokine Combinations (ICS): Plot of the Actual Values Over Time (CD4+); Cohort 1a; Per Protocol Immunogenicity Set (Study VAC31518COV1001)

3.3.2.1.4. Study COV1002 – Booster dose (second dose) at 2 or 3 Months

nAb and binding Ab results for 43 participants of Cohort 1 (≥20 to ≤55 years of age) and 48 participants of Cohort 2 (≥65 years of age) are available.

Graphical representations of neutralizing and binding antibody responses against SARS-CoV-2 over time (GMTs with corresponding 95% CIs) are presented in the *Figure 13* and *Figure 14*.

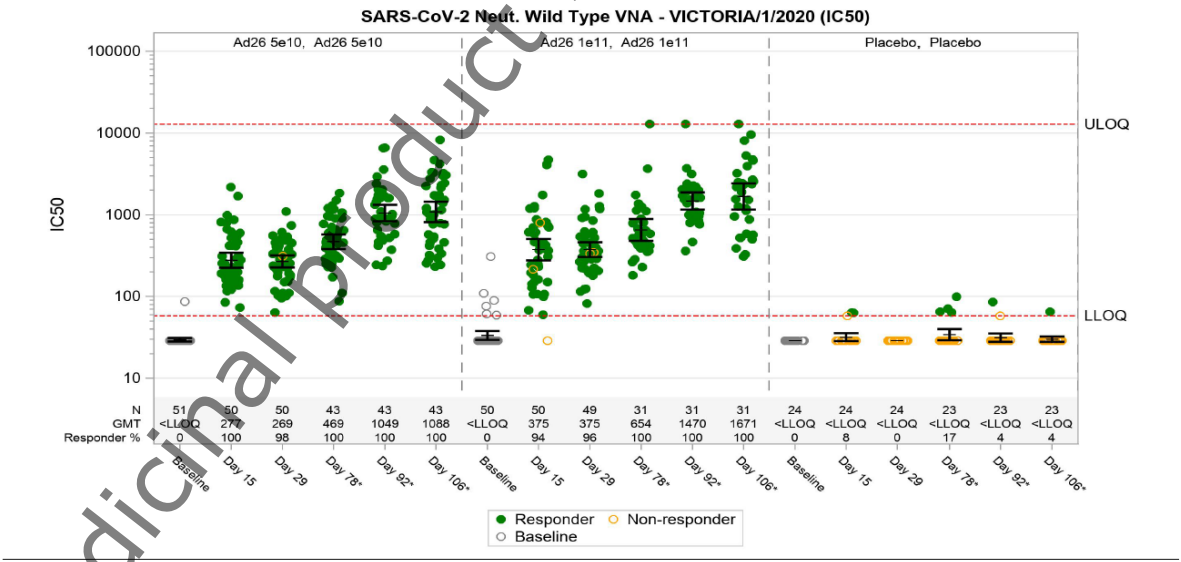
Because of the study pause, the second vaccine dose was administered 3 months after the first dose in the young adults (≥20 to ≤55 Years, Cohort 1) instead of 2 months post-dose 1. The second vaccine dose was administered according to the protocol, i.e. 2 months after the first dose, in the older adults (≥65 Years, Cohort 2) included in the study. Results can thus not be compared between both cohorts.

Results follow the same pattern than results observed in study COV1001. Neutralizing and binding Ab are increased post-dose 2 when compared to 1 month post-dose 1 and pre-booster dose (second dose).

In the younger adult cohort, pre-booster dose (second dose) (Day 78) GMT (95% CI) increases from 469 (382-576) to 1088 (817-1449) post-booster dose (second dose) (Day 106), resulting in a GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination of 2.3 (1.8-3.0).

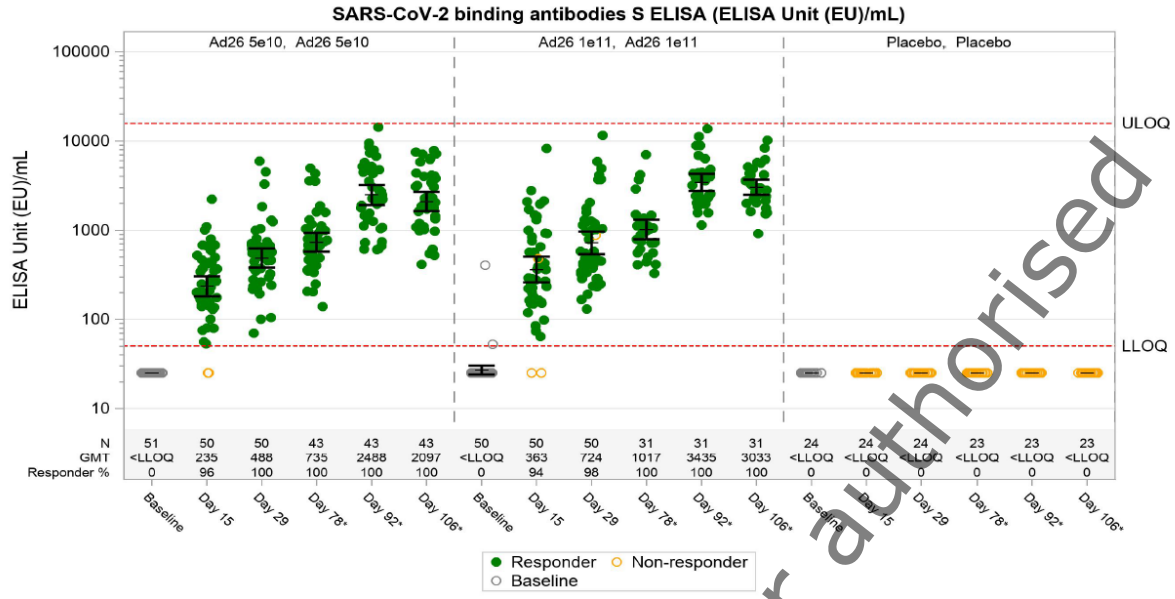
In the older adult cohort, pre-booster dose (second dose) (Day 57) GMT (95% CI) increases from 281 (204-386) to 429 (335-550) post-booster (second dose) (Day 85), resulting in a GMT (95% CI) fold-increase from pre-dose 2 to 1 month post-vaccination of 1.5 (1.1-2.0).

Since the GMT values pre-boost are different between cohorts, the magnitude of the response cannot be compared. It is not known if the Ab levels reached 1 month post-dose 2 will be sustained and for how long.



Note: Geometric mean titers with 95% CI shown in the 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.
The sensitivity analysis shows the second vaccination visit and subsequent visits as the median day (ie, Days 78, 92, and 106), which were the median number of days post dose 1 that the second vaccination was received and the actual subsequent visit dates in Cohort 1.
[GIRHUM61_SA1-C1.RTF] [VAC31518\VAC31518COV1002\DBR_PA1_CSR_SEQUESTERED\RE_CSR\PROD\GIRHUM61_SA1-C1.SAS] 02JUL2021, 13:17

Figure 13. SARS-CoV-2 neutralization wild type VNA – VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Sensitivity Analysis Based onActual Study Day; Cohort 1; Per Protocol Immunogenicity Set (Study VAC31518COV1002



Note: Geometric mean titers with 95% CI shown in the 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.
The sensitivity analysis shows the second vaccination visit and subsequent visits as the median day (ie, Days 78, 92, and 106), which were the median number of days post dose 1 that the second vaccination was received and the actual subsequent visit dates in Cohort 1.
[GIRHUM21_SA1-C1.RTF] [VAC31518\VAC31518COV1002\DBR_PA1_CSR_SEQUESTERED\RE_CSR\PROD\GIRHUM21_SA1-C1.SAS] 02JUL2021, 13:17

Figure 14. SARS-CoV-2 binding antibodies S ELISA (ELISA Unit (EU)/mL): Plot of the Actual Values Over Time; Sensitivity Analysis Based on Actual Study Day; Cohort 1; Per Protocol Immunogenicity Set (Study VAC31518COV1002)

3.3.2.2. Homologous Booster Vaccination 2 Months After Dose 1 (5×10^{10} vp, 5×10^{10} vp Dose Level) - VOCs

Neutralizing antibodies against the Alpha and Beta SARS-CoV-2 VOC after 2 doses of Ad26.COV2.S at the of 5×10^{10} vp level (56-day interval) were measured in a subset (n=6) of Day 71 (ie 14 days post-dose 2) samples from COV1001 Cohort 1a and compared to the values with the reference strain.

Ab titers are increased following the second vaccine dose. nAb titers against the Alpha variant following the second vaccine dose reached a comparable level than observed for the Victoria strain following the first vaccine dose. nAb titers post-dose 2 against the Beta variant remained low.

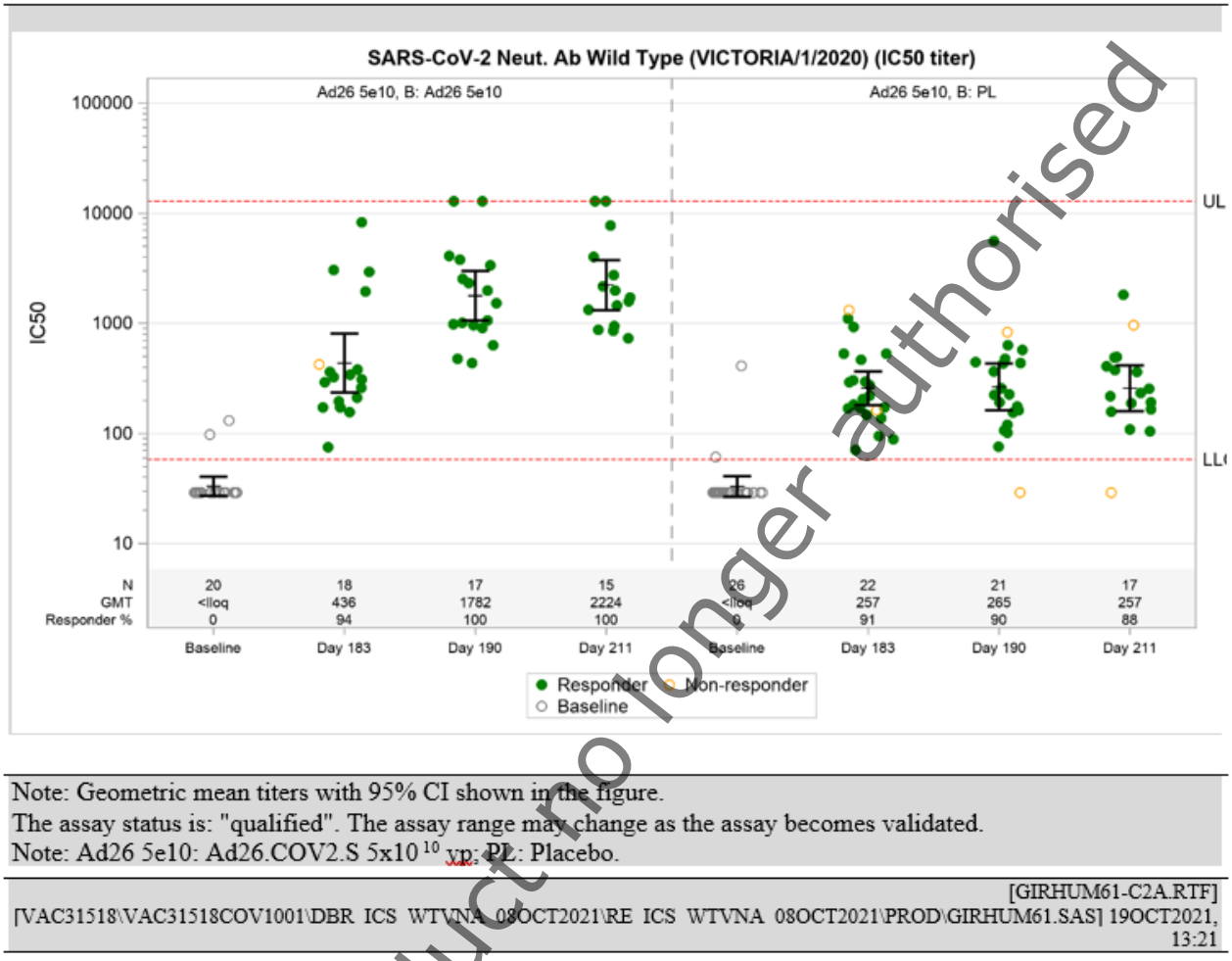
Data observed 6 months post-boost also indicate that nAb titers against different variants increased but remained at a level inferior to the one obtained with the prototype.

3.3.2.3. Homologous Booster Vaccination 6 Months After Dose 1 (5×10^{10} vp, 5×10^{10} vp Dose Level) - parental SARS-CoV-2 strain

In Cohort 2a (Group 2) of study COV1001, immunogenicity of a booster dose after the primary vaccination regimen was evaluated in healthy adults aged ≥18 to ≤55 years. Participants received Ad26.COV2.S at the selected dose level of 5×10^{10} vp as the first dose and received Ad26.COV2.S at a dose level of 5×10^{10} vp as the booster, 6 months (Day 183) after primary vaccination. Results are available for 17 participants.

nAb results were obtained by using two different psVNA (JBDA and Monogram). Results were further presented by using the wtVNA as these are considered the most relevant ones (*Figure 15*). Results were presented for the reference strain, but no data at Day 29 post-primary vaccination were provided. It is thus not know if the kinetic of the humoral response is similar to comparable groups of other studies.

Data show an increase in nAb post-boost, up to Day 211 (14 days after the boost). GMT (95% CI) increased from 436 (235-807) pre-boost to 2224 (1319-3750) at Day 211, resulting in a fold increase of 4.4 (2.7-7.1).



Note: Geometric mean titers with 95% CI shown in the 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; PL: Placebo.

[GIRHUM61-C2A.RTF]
[VAC31518\VAC31518COV1001\DBR ICS WTVNA 08OCT2021\RE ICS WTVNA 08OCT2021\PROD\GIRHUM61.SAS] 19OCT2021, 13:21

Figure 15. SARS-CoV-2 neutralization wild type VNA – VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Cohort 2a; Per Protocol Immunogenicity Set (VAC31518COV1001)

Binding Ab results are available by using the S-ELISA from Nelexis and JBDA. Binding Ab GMT (95% CI) increases from 798 (441-1443) pre-boost to 3779 (2583-5529) and 5108 (3402-7669) 7 and 14 days post-boost, respectively. 95% CIs post-boost are wide.
It is also important to note that, before the boost, at Day 183, Ab titers are not comparable between the group of subjects having received the boost ($5x10^{10}$ vp, $5x10^{10}$ vp) and the group of subject having received the placebo as second dose ($5x10^{10}$ vp, placebo). GMTs (95% CI) are respectively 798 (441-1443) and 490 (349-689). So, even if a booster effect is observed post-injection of the Janssen COVID-19 vaccine, it is considered that the magnitude of the response could not be representative.

A Non-inferiority post-hoc analysis of both the nAb and binding Ab responses was performed on the 17 subjects. Since there was no decrease pre-boost when compared to 1 month post-dose 1, the results are not considered relevant, even if NI was formally demonstrated. Results are thus not presented.

3.3.2.4. Homologous Booster Vaccination 6 Months After Dose 1 ($5×10^{10}$ vp, $5×10^{10}$ vp Dose Level) - VOCs

Samples from a subset of Cohort 2a participants from study COV1001, who had received a 6 month booster vaccination (n=17), were measured for neutralizing antibodies against the SARS-CoV-2 Beta,

Gamma (P.1 lineage), Delta, and Lambda (C.37 lineage) variants by a psVNA (assay status: developed) conducted by Janssen Bioassay Development and Automation (JBDA), prior to booster (Day 183), as well as 7 days (Day 190) and 28 days (Day 211) after booster. Further results were presented for the Beta strain with the partial validated psVNA of Monogram.

Overall, for all the VOCs, and increase of Ab titers is observed post-boost, as early as 7 days after the boost. Slight increases are observed from 7 days to 14 days post-boost. nAb levels at Day 211 were higher for the Delta and Lambda strains, and lower for the Gamma and Beta strains. nAb levels observed at Day 211 for the variants are lower than the one observed for the parental strain. Post-boost levels for the variants appears to be similar or higher than the pre-boost Ab level for the parental strain. However the Ab level pre-boost for the parental strain was low (GMT and [95% CI] of 32 [<LOD-67]). The Ab level 1 month post-dose 1 would have been more informative, but results are not available. In addition, as it is likely that the psVNA lacks of sensitivity, measurement with a test with adequate performance would have been preferred.

Binding Ab (JBDA ELISA) were also measured against the SARS-CoV-2 Beta and Delta variants in the samples of the 17 subjects. Results from Baseline, Day 29, Day 183, Day 190 and Day 211 samples are available. Similarly than for the nAb, binding Ab were increase post-boost.

Overall, whether these (low) Ab levels reached post-boost would translate in clinical protection is not known. It is not known either if these Ab levels will be maintained over time, and for how long.

3.3.2.5. Homologous Booster Vaccination 6 Months After Dose 1 (5×10^{10} vp, 1.25×10^{10} vp Dose Level) - parental SARS-CoV-2 strain

Anamnestic responses after antigen presentation at a dose level of 1.25×10^{10} vp were evaluated in the participants of group 5 of study COV2001. The booster dose was given 6 months post-vaccination (1 single dose, 5×10^{10} vp). Binding Ab (S-ELISA) responses post-vaccination are available for 71 subjects, including 43 vaccinees of 18-55 yoa and 28 of ⩾65 yoa (n at 7 days post-boost). Neutralizing Ab were not measured.

The low dose exposure allows evaluation of the memory response to the S protein. It can also act as a booster dose.

Overall, an anamnestic response is observed, as fast as 7 days post-exposure.

In the younger adult group, GMT (95% CI) increased from 416 (294-588) at Day 169 to 1719 (1321-2236) at Day 176 and to 2444 (1855-3219) at Day 197.

Seven days after the boost, GMTs were lower in the older adult group, but tend to be similar at 28 days post-boost. Day 169-GMT (95% CI) was 234 (136-403), Day 176-GMT (95% CI) was 687 (404-1168), and Day 197-GMT (95% CI) was 2048 (1290-3253). 95% CIs are wide, reflecting the small number of samples included in the analysis (n=28).

Proportions of responders were high and similar pre-and post-boost in both age groups.

3.3.3. Impact of Neutralizing Antibodies Against Ad26 Vector

Theoretically, nAb to the Ad26 vector generated post-dose 1 may have the potential to negatively impact responses to Ad26.COV2.S post-dose 2. Therefore, nAb to the Ad26 vector were measured in study COV1001 (Cohort 1a; Group 1 and Group 3; i.e., 2 doses of Ad26.COV2.S at the 5×10^{10} vp and

1×10^{11} vp dose levels, respectively, with a 56-day interval), by the Ad26 VNA at baseline and prior to second vaccination on Day 57.

Results of 24 and 23 18-55 yoa participants that received the lower (5×10^{10} vp) or the higher (1×10^{11} vp) dose levels, respectively, were included in the analysis. Only 1 sample was positive for Ad26 nAb at baseline whereas 100% of the samples were positive for Ad26 nAb pre-dose 2.

Correlation analysis of Ad26 neutralizing antibodies pre-dose 2 compared to SARS-CoV-2 neutralizing antibodies post-dose 2 were calculated. Spearman r was -0.3178 and -0.2112 at Day 85 and Day 239 post-primary vaccination, respectively.

Since none of the samples were negative, the magnitude of the insert specific vaccine-elicited humoral immune responses post-dose 2 cannot be compared between Ad26 nAb positive and negative samples. The booster dose (second dose) of the vaccine is able to induce and increase in Ab titers, but it is not known if the magnitude of the responses is impacted by the Ad26 nAb-induced by the first vaccine dose. The impact on binding Ab and T cell responses was not presented.

The MAH referred to further supporting data from the COV1002 study. Ad26 nAb results of 51 and 50 participants of, respectively, cohorts 1 and 2, vaccinated with the dose level of 5×1010 vp, are available as well as results of 50 and 49 participants of, respectively, cohorts 1 and 2, vaccinated with the dose level of 1×1011 vp. However Ad26 nAb were only measured at baseline and not post-dose 1. Only four samples of cohort 1 were positive at baseline for natural Ad26 nAb. Twenty-six samples from cohort 2 were positive at baseline for natural Ad26 nAb. The correlation between Ad26 nAb at baseline and SARS-CoV-2 nAb post-dose 1 was poor. The correlation analysis of Ad26 nAb at baseline compared to SARS-CoV-2 nAb post-dose 2 are not considered fully relevant. The performed analyses do no assess the impact of the Ad26 nAb-induced by the vaccine, but rather by the natural infection, on the SARS-CoV-2 nAb-induced by the vaccine.

Overall, the conclusion raised at conditional MA remained unchanged. The potential impact of natural or vaccine induced pre-existing anti-Ad26 immunity on immunogenicity and vaccine efficacy remains unclear and should be further documented. This is even more important if regular boosters are needed. Integrated results of the different trials included in the COVID-19 CDP, and overall for Ad26-based vaccination, if possible, are further expected.

3.3.4. Correlation Between Neutralizing and Binding Antibody Responses

Correlation Between Neutralizing Antibodies and Binding Antibodies

Correlation between nAb titers (IC_{50}), measured by the wtVNA, and binding Ab concentrations (EU/mL), measured by S-ELISA for the reference strain, were calculated in samples from study COV1001 (Cohorts 1a and 3), all dose levels and regimens:

- The Spearman correlations for Cohort 1a are: Day 29: 0.84; Day 71: 0.92; Day 85: 0.88; and Day 239: 0.84
- The Spearman correlations for Cohort 3 are: Day 29: 0.71; Day 71: 0.87; Day 85: 0.92; and Day 239: 0.84.

There is a good correlation between both assays with a Spearman correlation ≥0.70, independent of the timepoint.

Several samples in Cohort 3 have a value below the LLOQ for the wtVNA assay, while the value is >LLOQ for the ELISA on Day 239.

The MAH also refer to the correlation results of study COV1002. The Spearman correlation for Cohort 1, from Day 15 to Day 85, was >0.65. For Cohort 2, the Spearman correlation was >0.70.

As a consequence, the conclusion reached at initial conditional MA remained, i.e. results should be confirmed on samples from the Phase 3 trial, including participants of various countries and with comorbidities. Pooled analyses might be of added value. Meanwhile, both wtVNA and binding Ab results are needed to characterize the vaccine-induced immune responses.

3.3.5. Heterologous Booster Vaccination With Ad26.COV2.S (5×10^{10} vp) - parental SARS-CoV-2 strain

3.3.5.1. Introduction

Phase 1/2 study DMID 21-0012, an ongoing heterologous platform boost study conducted by NIH/NIAID in the US (also referred to as Mix and Match study), is evaluating the immune responses in adult participants who received a homologous or heterologous booster vaccination at least 12 weeks after primary vaccination with an approved mRNA COVID-19 vaccine regimen (2 doses of Moderna-mRNA-1273 [100 µg] or 2 doses of Pfizer/BioNTech-BNT162b2 [30 µg]) or Ad26.COV2.S [1 dose 5×10^{10} vp]. Interim results are published in Atmar and Lyke 2021. The MAH presented data from the groups who received one dose of COVID-19 Vaccine Janssen as booster vaccination. Additional data considered relevant by the Rapporteur for this application will also be discussed hereafter.

3.3.5.2. Methods

3.3.5.2.1. Study design

This is a phase 1/2, open-label clinical trial in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273; mRNA-BNT162b2; or Ad26.COV2.S). This is an adaptive design and may add arms (and increase sample size) as vaccines are awarded EUA and/or variant lineage spike vaccines are manufactured or become available. Enrollment is occurring at approximately twelve domestic clinical research sites.

This study includes two cohorts. This report includes data of Cohort 1, which is designed to provide rapid information about the safety, reactogenicity, and immunogenicity of delayed boost. The report presented by the MAH focusses only on the groups who received one dose of COVID-19 Vaccine Janssen as booster vaccination (group 4E, 5E, 6E who received as primary vaccination COVID-19 vaccine Janssen, Spikevax and Comirnaty, respectively). Cohort 2 is an adaptive cohort that is evaluating, in a prospective fashion, the safety, reactogenicity and immunogenicity of EUA-dosed vaccine followed by delayed boost. Pools of subjects will be recruited to receive EUA-dosed vaccine and will be assigned, at a later date, to a delayed booster vaccine based on availability of vaccine product, to enable rapid implementation based on situational assessment of need. Data of Cohort 2 are not available.

1. Previously EUA-dosed vaccination with Janssen – Ad26.COV2.S at $5x10^{10}$ vp followed by:

- Group 1E – A 100-mcg dose of mRNA-1273
- Group 4E – A $5x10^{10}$ vp dose of Ad26.COV2.S
- Group 7E – A 30-mcg dose of BNT162b2

- Group 10E – A 100-mcg dose of mRNA-1273.211
- Group 12E – A 50-mcg dose of mRNA-1273

2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by:

- Group 2E – A 100-mcg dose of mRNA-1273
- Group 5E – A $5x10^{10}$ vp dose of Ad26.COV2.S
- Group 8E – A 30-mcg dose of BNT162b2
- Group 13E – A 50-mcg dose of mRNA-1273

3. Previously EUA-dosed vaccination with Pfizer/BioNTech - mRNA-BNT162b2 at 30 mcg for two doses followed by:

- Group 3E – A 100-mcg dose of mRNA-1273
- Group 6E – A $5x10^{10}$ vp dose of Ad26.COV2.S
- Group 9E – A 30-mcg dose of BNT162b2
- Group 11E – A 100-mcg dose of mRNA-1273.211
- Group 14E – A 50-mcg dose of mRNA-1273

The anticipated sample size of each group is approximately 25 subjects 18 through 55 years of age and approximately 25 subjects 56 years of age and older for a total of 50 subjects per group. Because of this relatively limited sample size, analyses are descriptive and data should be interpreted with caution.

Subjects in Cohort 1 did receive a single intramuscular (IM) injection of the designated delayed booster vaccine and will be followed through 12 months after vaccination. A telephone visit will occur at Day 8 and in-person follow-up visits will occur on Days 15 and 29, as well as 3, 6, and 12 months after the vaccination. Reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays.

Inclusion and exclusion criteria have not been presented by the MAH. All participants are individuals 18 years of age and older, who are in good health, have no reported history of COVID-19 or SARS-CoV-2 infection or monoclonal antibody infusion. As described in the publication of Atmar et al., no screening was done for past or current evidence of SARS-CoV-2 infection, which implies that participants with (history of) an asymptomatic infection could have been enrolled in the study.

Statistical methods have not been presented by the MAH. The publication Atmar et al. described that no statistical comparisons between groups were planned and the analyses of safety and immunogenicity endpoints are only descriptive. The selected sample sizes of 50 per group and 25 per age stratum, allow for 99.5% and 92.8% probability of observing at least one an AE with a true event rate of 10%, respectively. Confidence intervals were not adjusted for multiplicity.

3.3.5.2.2. Endpoints

The primary endpoints of the study are IgG serum binding antibody responses to the S-2P-WA-1 (wild type) and beta variant (S-2P-B.1.351) antigens, as obtained from the 4-plex ECLIA V.2 assay. Exploratory Endpoints include IgG serum binding antibody levels for two VOC: delta (S-2P-B.1.617.2) and alpha (S-2P-B.1.1.7), with S-2P-WA-1 as control.

Endpoints related to neutralization are ID50 and ID80 neutralization titers assessed with Spike-pseudotyped viruses. This report provides only data on neutralization titers specific to the Spike-

pseudotyped virus SARS-CoV-2 D614G. Neutralization titers specific to the Delta and Beta variant will be assessed, but are currently not yet provided. These data should be provided when available (refer to annex: new recommendations introduced in this procedure).

This report only includes data of Day 1 (pre-boost) and Day 15 (14 days post-boost). During this procedure, the MAH shared unpublished data of Day 29 nAb titers of the NIH study.

3.3.5.3. Results

3.3.5.3.1. Study participants

The data discussed in the report provided by the MAH focusses only on the cohorts who received a booster vaccination with COVID-19 vaccine Janssen after primary vaccination with the same vaccine, Spikevax (Moderna) or Comirnaty (Pfizer/BioNTech) (Groups 4E, 5E and 6E, respectively). In these groups, 50, 49 and 51 participants are enrolled, respectively.

Binding and neutralizing antibody data is available of all participants on Day 1 and of all except one in group 6E (prime vaccination with Comirnaty) on Day 15.

More detailed characteristic of participants enrolled in the study have been described in the publication by Atmar et al. Baseline characteristic of participants in the 3 concerned groups were similar: median age of approximately 50 years; at least 30% of each gender; and majority are white.

The mean interval between primary and booster vaccination was 17.7 weeks, 19.3 weeks and 20.6 weeks in the groups who were primary vaccinated with COVID-19 vaccine Janssen, Spikevax and Comirnaty, respectively.

It is stated in the publication that two participants (one each in the group primary vaccinated with COVID-19 vaccine Janssen and with Comirnaty) who had serologic evidence of prior SARS CoV- 2 infection and one participant (primary vaccinated with Spikevax) who developed COVID-19 two days prior to Study Day 29 were included in the analyses. As this is only one participant in each group, the impact on the results is considered negligible.

3.3.5.3.2. Immunogenicity results

Neutralizing Antibodies

Prior to booster administration on Day 1, nAb to the D614G strain could be measured in all participants who were primary vaccinated with Spikevax; 39 out of 50 subjects vaccinated with COVID-19 vaccine Janssen and 49 out of 51 subjects vaccinated with Comirnaty. Serum neutralization antibody titers (ID50) against Pseudovirus D614G prior to booster vaccination were highest in the Spikevax group (5E: GMT [95% CI]: 254.91 [185.86-349.62]), followed by Comirnaty (6E: 76.63 [55.25-106.28]) and COVID-19 vaccine Janssen (4E: 31.27 [20.13-48.57]).

On Day 15 after a booster with COVID-19 vaccine Janssen, nAb were increased in all groups compared to baseline. All, except one participant in the homologous boost group, had detectable nAb levels. Similar as for baseline nAb titers, after the booster vaccination, highest titers (ID50) are observed in the groups primary vaccinated with an mRNA vaccine (Spikevax: 1578.80 [1200.37-2076.54]; Comirnaty: 894.14 [652.14-1225.94]). Homologous boosting with COVID-19 Vaccine Janssen resulted in lower titers (129.85 [92.05-183.17]). In addition, also the fold increase in nAb titers after the boost were highest in the group who received an mRNA vaccine as primary vaccination (Spikevax: 6.19 [95% CI: 4.49-8.54];

Comirnaty: 12.50 fold [95% CI: 8.74-17.87]) compared to the group primed with COVID-19 vaccine Janssen (4.15 [2.97-5.80]).

No meaningful differences are observed between the two age groups (18–55 yoa and ≥56 yoa) in pre- and post-boost nAb GMTs, with 95% CIs always largely overlapping.

The same trend is observed for the ID80 nAb titer evaluation.

Data on neutralizing capacity of the Delta and Beta variant is currently not yet available.

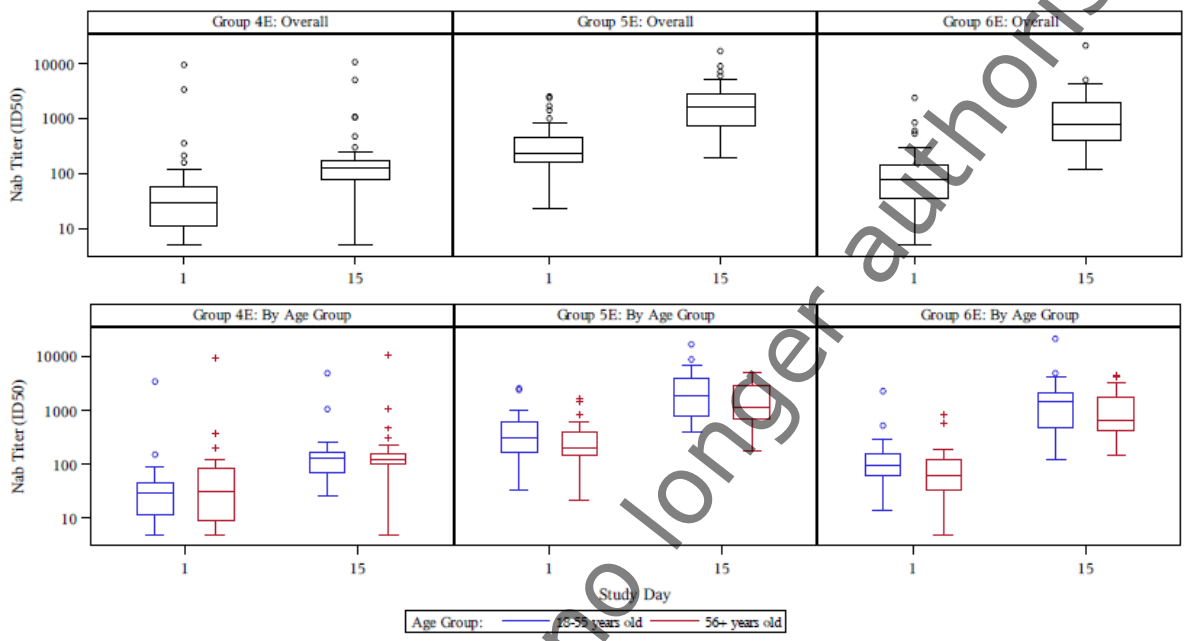


Figure 16. Neutralization Antibodies Titer (ID50) to Pseudovirus D614G, by Group, Age Group, and Timepoint - Groups 4E - 6E

Additional data of the same study have been published by Atmar et al. including data of groups who were boosted with an mRNA vaccine, 3 months after primary vaccination with either COVID-19 Vaccine Janssen, Spikevax or Comirnaty. In this publication, nAb titers are presented in International Units ID50 (IU50/mL) by using a conversion factor of 0.242. The data show that, in participants primary vaccinated with COVID-19 vaccine Janssen, nAb GMTs (95% CI) on Day 15 are much higher after a heterologous boost with an mRNA vaccine (Spikevax: 676.1 [517.5 – 883.3]; Comirnaty: 341.3 [239.6 – 486.3]) compared to a homologous boost (31.42 [22.3 - 44.3]). The fold increase in nAb titers in participants vaccinated with COVID-19 vaccine Janssen as primary vaccination is much higher after heterologous boost with an mRNA vaccine compared to a homologous boost (36- and 76-fold increase after boosting with Comirnaty and Spikevax, respectively). Similarly, also for participants who received an mRNA vaccine as primary vaccination, boosting with an mRNA vaccine resulted in higher nAb levels compared to boosting with COVID-19 vaccine Janssen.

During the assessment of this procedure, the MAH shared unpublished data of Day 29 nAb titers of the NIH study (Table 8). Similar as on Day 15, Day 29 data show that in participants primary vaccinated with COVID-19 vaccine Janssen, nAb GMTs (IU50/mL; 95% CI) are much higher after a heterologous boost with an mRNA vaccine ((Spikevax: 431.7 [322.6-577.6]; Comirnaty: 242.4 [189.9-309.4]) compared to a homologous boost (29.7 [22.3-39.6]). Of note, compared to Day 15, Day 29 nAb GMTs remained stable in the COVID-19 vaccine Janssen homologous boost group, while after a heterologous boost with an mRNA vaccine, nAb titers decreased.

When heterologous boosting with COVID-19 Vaccine Janssen in participants primary vaccinated with an mRNA vaccine, there is a trend for further increase in nAb by Day 29 compared to Day 15 (Spikevax: 528.4 [3831-728.9]; Comirnaty: 266.8 [196.5-362.3]). However, boosting with an mRNA vaccine results in a decrease in nAb titers by Day 29 compared to Day 15, irrespective of the vaccine used for primary vaccination. While there was a clear difference in nAb titers on Day 15, on Day 29, nAb GTMs are roughly similar (with overlapping 95% CI) after a homologous boost with an mRNA vaccine (Spikevax: 700.0 [568.6-861.8]; Comirnaty: 306.1 [244.2-383.6]) compared to a heterologous boost with COVID-19 vaccine Janssen after primary mRNA vaccination (Spikevax: 528.4 [383.1 – 728.9]; Comirnaty: 266.8 [196.5-362.3]). Of note, the booster dose used for Spikevax was the double of the authorized dose in EU. It could be that this influenced the results and that the response to a 100 µg booster is higher than the response to a 50 µg booster.

Table 8 National Institute of Allergy and Infectious Diseases (NIAID) MixNMatch Phase 1/2 Study - Pseudovirus Antibody Titers Including Day 29 (Unpublished Data shared by the MAH)

Group	1	2	3	4	5	6	7	8	9
Primary EUA Immunization	Janssen	Moderna	Pfizer/BioNTech	Janssen	Moderna	Pfizer/BioNTech	Janssen	Moderna	Pfizer/BioNTech
Vaccine	Ad26.COV2-S	mRNA-1273	BNT162b2	Ad26.COV2-S	mRNA-1273	BNT162b2	Ad26.COV2-S	mRNA-1273	BNT162b2
	$5x10^{10}$ vp	100-mcg	30-mcg	$5x10^{10}$ vp	100-mcg	30-mcg	$5x10^{10}$ vp	100-mcg	30-mcg
Booster	Moderna mRNA-1273 100-mcg			Janssen Ad26.COV2-S $5x10^{10}$ vp			Pfizer/BioNTech BNT162b2 30-mcg		
Pseudovirus Neutralizing Antibody Titers (International Unit 50% (IU_{50})/mL)									
D614G ‡									
Day 1 GMT (95% CI)	8.9 (6.2-12.8)	88.7 (67.7-115.9)	24.8 (18.0-34.2)	7.6 (4.9-11.8)	61.7 (45.0-84.6)	18.6 (13.4-25.7)	9.4 (6.4-13.6)	57.6 (45.0-73.7)	21.4 (15.3-30.0)
Day 15 GMT (95% CI)	676.1 (517.5-883.3)	901.8 (727.5-1117.8)	785.8 (596.4-1035.2)	31.4 (22.3-44.3)	382.1 (290.5-502.5)	216.4 (157.8-296.7)	343.5 (243.6-484.4)	693.6 (578.0-832.2)	437.2 (333.8-572.5)
Day 29 GMT (95% CI)	431.7 (322.6-577.6)	700.0 (568.6-861.8)	495.7 (370.4-663.4)	29.7 (22.3-39.6)	528.4 (383.1-728.9)	266.8 (196.5-362.3)	242.4 (189.9-309.4)	515.2 (436.1-608.7)	306.1 (244.2-383.6)
Percentage with four-fold rise at Day 15 (95% CI)	100.0% (93.2%-100.0%)	86.0% (73.3%-94.2%)	100.0% (92.9%-100.0%)	50.0% (35.5-64.5%)	61.2% (46.2-74.8%)	82.0% (68.6-91.4%)	98.1% (89.7-100.0%)	94.1% (83.8-98.8%)	98.0% (89.1-99.9%)
Day 15 geometric mean fold rise (95% CI)	75.9 (55.0-104.8)	10.2 (8.0-12.8)	31.7 (23.8-42.2)	4.2 (3.0-5.8)	6.2 (4.5-8.5)	12.5 (8.7-17.9)	36.4 (25.0-52.9)	12.0 (9.4-15.4)	20.0 (14.6-27.4)

* GMT- Geometric mean titers

† CI- Confidence Intervals. The confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for

Binding Antibodies

Binding Antibodies are evaluated on Day 15 after boosting with Ad26.COV2.S (5×10^{10} vp) and compared to Day 1 (pre-boost). Antibody responses are assessed against WA-1 antigen, B.1.351 Antigen (Beta variant), B.1.1.7 and B.1.617.2 (Delta Variant) (Table 9).

All participants had detectable binding Ab to the **WA-1 strain** prior to booster administration on Day 1, approximately 18 to 21 weeks after primary vaccination, analyzed with the 4-plex ECLIA. Participants who received COVID-19 vaccine Janssen as primary vaccination had the lowest baseline binding Ab GMTs (7919.93 AU/mL) compared to participants who had an mRNA vaccine as primary vaccination. Baseline binding Ab titers were higher in participants vaccinated with Spikevax (70971.97 AU/mL) compared to Comirnaty (35625.45 AU/mL). No significant differences in baseline binding Ab titers are observed between the two age groups (18 – 55 yoa and ≥56 yoa).

An increase in binding Ab levels following a boost with COVID-19 vaccine Janssen was observed in all groups by Day 15. Similar as for baseline binding Ab titers, after the booster vaccination, highest titers (95% CI) are observed in the groups primary vaccinated with an mRNA vaccine (Spikevax: 336599.73 AU/mL [270353.77-419078.23]; Comirnaty: 211637.19 AU/mL [166422.09-269136.75]). Homologous

boosting with COVID-19 Vaccine Janssen resulted in lower binding Ab levels (36219.34 AU/mL [26195.90-50078.09]. In terms of fold increase in binding Ab titers post-boost vs. pre-boost, no meaningful differences are observed between groups (all 95% CIs are overlapping).

It was mentioned in the Immunogenicity Summary report that binding Ab responses further increased by Day 29, reaching a 5.3 fold, 7.0 fold and 7.9 fold increase versus baseline in participants who had primary vaccination with COVID-19 vaccine Janssen, Spikevax or Comirnaty, respectively. However, the data were not provided.

Baseline binding Ab titers against the **B.1.351 Antigen (Beta-variant)** are lower compared to the WA-1 antigen, but relative differences between the type of vaccine used as primary vaccination is similar. Participants who received COVID-19 vaccine Janssen as primary vaccination had the lowest baseline binding Ab GMTs (2924.81 AU/mL) compared to participants who had an mRNA vaccine as primary vaccination. Baseline binding Ab titers were higher in participants vaccinated with Spikevax (28906.08 AU/mL) compared to Comirnaty (17257.52 AU/mL). After the booster vaccination, GMTs increased to 15031.97 AU/mL (10075.70-22426.24); 138257.72 AU/mL (110105.02-173608.78); and 99536.65 AU/mL (77764.17-127405.01), respectively. The same trend is followed as for binding Ab titers against the WA-1 antigen.

Baseline antibody titers to the **Delta and Alpha variants**, analyzed with the 10-plex ECLIA assay, are lower compared to the WA-1 antigen. After boosting with COVID-19 vaccine Janssen, GMT increased, reaching the highest Ab levels against both variants in the group who received Spikevax as primary vaccination, followed by the group who received Comirnaty, and Ab levels were lowest in the homologous booster group.

Overall, for all the variants, no meaningful differences are observed between the two age groups (18 – 55 yoa and ≥56 yoa) in pre- and post-boost binding Ab GMTs, with 95% CIs always largely overlapping.

The publication of Atmar et al. (see above) also includes data on binding Ab in the groups who were boosted with an mRNA vaccine after primary vaccination with either of the 3 vaccines. Neutralizing Ab titers are presented in Binding Antibody Units (BAU)/mL, instead of IU50/mL, by using a conversion factor of 0.009. In participants primary vaccinated with COVID-19 vaccine Janssen, binding Ab GMTs (95% CI) to WA-1 antigen on Day 15 are much higher after a heterologous boost with an mRNA vaccine (Spikevax: 3203.1 BAU/mL [2499.5 – 4104.9]; Comirnaty: 2549.5 BAU/mL [2038.1 – 3189.3]) compared to a homologous boost (326.0 BAU/mL [235.8 – 450.7]). Similarly, also for participants who received an mRNA vaccine as primary vaccination, boosting with an mRNA vaccine results in much higher binding Ab levels compared to boosting with COVID-19 vaccine Janssen. This is not only the case for the WA-1 antigen, but also for B.1617.2 (Delta).

Table 9 *Variants of Concern: IgG Serum Binding Antibody Response to S-2P-B.1.617.2 (Delta Variant) by FFP 10-plex ECLIA. Results are reported as Area Under Curve (AUC)*

Primary Boost	Janssen (N=52) Spikevax (N=52)	Spikevax (N=50) Spikevax (N=50)	Comirnaty (N=50) Spikevax (N=50)
Delta (B.1.617.2)	GMT (95% CI)		
Day 1 (Pre-boost)	1429.94 (1118.13-1828.70)	15172.76 (12772.45-18024.15)	7696.02 (6085.21-9733.22)
Day 15	40907.72 (37505.30-44618.81)	50557.92 (48214.00-53015.79)	48494.17 (44985.03-52277.04)

Primary Boost	Janssen (N=53) Comirnaty (N=50)	Spikevax (N=51) Comirnaty (N=48)	Comirnaty (N=50) Comirnaty (N=48)
Delta (B.1.617.2)	GMT (95% CI)		
Day 1 (Pre-boost)	1845.42 (1385.10-2458.72)	12196.16 (10499.06-14167.57)	6454.35 (5287.39-7878.87)
Day 15	35446.38 (31962.21-39310.35)	45451.87 (43014.66-48027.17)	39405.78 (36050.51-43073.32)

3.4. Discussion

Results from several studies were included as key data to support of the proposed homologous booster Variation: the First-in-human trial COV1001, Phase 1 and 2 studies COV1002 and COV2001 and the Phase 3 trial COV3009.

- Study **COV1001** is an ongoing randomized, double-blind, placebo-controlled, Phase 1/2a multicenter FIH dose selection study conducted in adults aged 18 to 55 years and aged 65 years or older in Belgium and in the US. This study also includes evaluation of a single booster vaccination.
- Study **COV1002** is a randomized, double-blind, placebo-controlled, Phase 1 trial in adults aged 20 to 55 years and 65 years or older. Two dose levels were tested in a 2-dose schedule in Japan.
- Study **COV2001** is an ongoing randomized, double-blind, placebo-controlled, multicenter Phase 2a study conducted in Germany, the Netherlands and Spain. Healthy adolescents (12 to 17 yoa), adults aged 18 to 55 years, and adults aged 65 years and older were enrolled. Immunogenicity of Ad26.COV2.S in 1- and 2-dose vaccination regimen is evaluated across a range of dose levels and vaccination intervals. The primary vaccination is followed by a single low-dose immunization after 4 months (2-dose regimen) or 6 months (single-dose regimen) to assess the immune memory.
- Study **COV3009** is a randomized, double-blind, placebo-controlled, multi-country trial Phase 3 study to assess the efficacy, safety and immunogenicity of a two-dose Ad26.COV2.S, given 56 days apart, for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. Complete immunogenicity results of COV3009, including a higher number of samples, as well as longer-term timepoints (e.g. 6-months post-dose 2), are expected to be available for MAH assessment in Q2 2022.

Data from the dedicated booster study conducted by the MAH (**COV2008**) are not not yet available. This study is ongoing and is assessing the immune responses following administration of a boost with the COVID-19 Vaccine Janssen in individuals vaccinated at least 6 months before with a single dose of the COVID-19 Vaccine Janssen or with 2 doses of the Pfizer vaccine, Comirnaty. Results of the primary analysis of COV2008 are expected to be available by February/March 2022. However, preliminary results from the study COV2008 were submitted during the procedure. See below '*Immune responses*

following 1 dose of the COVID-19 Vaccine Janssen in subjects primary vaccinated with mRNA vaccines'. Data on the durability of the immune responses from the **COV3001** are not submitted yet.

Study results from the Phase 1/2 study **DMID 21-0012**, an ongoing heterologous platform boost study conducted by NIH/NIAID in the US (also referred to as Mix and Match study, published in Atmar and Lyke 2021) were also included and supports this variation. The MAH presented data from the groups who received one dose of COVID-19 Vaccine Janssen as booster vaccination. Additional data (published in Atmar et al.) considered relevant are also discussed in the assessment.

With the exception of study COV3009, the methods of the above-mentioned studies were already assessed at initial conditional MA. Please refer to the efficacy section for the COV3009 methods.

Thus, the data package consists of data from different studies, each including a limited number of vaccinated subjects and that vary by timepoints (higher number of subjects at Day 29 than at Day 169 for example).

Long-term immunogenicity results following a single dose of Ad26.COV2.S at the 5×10^{10} vp dose level was submitted to support the need for booster. The effect of a second/booster dose, given at 2, 3 and 6 months after primary vaccination (at 5×10^{10} vp or 1.25×10^{10} vp dose levels) were evaluated in different studies. **COV2001** is the only study where immune responses after booster vaccination can be compared between a 2- or 3-month time-interval since primary vaccination, within groups of the same age range.

For most of the studies, neutralizing and binding Ab results are available, overall and by age category (younger adults of 18/20-55/59 yoa and older adults of ≥60/65 yoa). Limited data on the characterization of functional Ab (ADCP) and on cellular immune responses are presented for study **COV1001.**

Most of the results are for the original Victoria strain. Limited results are presented for the variants of concern (VOC). There are no data for the Delta or Mu variant.

The immunogenicity analyses are descriptive and were performed on the per protocol immunogenicity (PPI) population (i.e. all randomized and vaccinated participants for whom immunogenicity data are available), unless specified otherwise. Sensitivity analyses, based on the Full Analysis Set (FAS) (all randomized participants who received at least 1 dose of study vaccine), were performed for Cohort 3 of study **COV1001** and of Cohort 1 of study **COV1002**. This is because, due to a pause implemented across studies in the Ad26.COV2.S clinical development program, blood draw for immunogenicity and vaccination were delayed, for approximately 1 month, for the majority of COV1001 Cohort 3 (≥65 yoa) participants and of COV1002 Cohort 1 (20-55 yoa) participants. Blood draw and vaccination occurred according to the protocol for COV1001 Cohort 1a (18-55 yoa) and COV1002 Cohort 2 (≥65 yoa). Results can thus not be compared between both the younger adult and the older adult cohorts of each study because of the difference of the time interval between doses. Similarly, no comparison of the results obtained post-dose 2 either at 2 or 3 months post-dose 1 can be made since the age groups were not comparable between schedule.

Immunogenicity assays

Most of the nAb and binding Ab results presented for the parental strain were obtained by using the qualified wtVNA from PHE and the validated S-ELISA from Nelexis. Performance of both assays was assessed at initial conditional MA. Results obtained with the validated psVNA from Monogram were also presented but correlation with the wtVNA was low to moderate (limited n of samples include in the

analysis). Results presented for the variants were obtained by using a developed psVNA by JBDA and/or a partly validated psVNA from Monogram. Both assays seem to lack sensitivity. Some results obtained with a S-ELISA developed by JBDA were also presented. ADCP and CMI data were obtained by using the same assays than those assessed at initial conditional MA.

Study DMID 21-0012 results were obtained by using a validated psVNA from Duke nAb LAb and 4- or 10-plex ECLIA assay at final stage of validation and fit-for-purpose, respectively, for the measurement of binding Ab specific to the parental strains or variants.

A number of recommendations related to the immunologocial assays are introduced in this procedure (refer to Annex).

Participant information

Participant information for the studies **COV1001** Cohort 1a (N=377) and Cohort 3 (N=403); **COV1002** (N=125) and **COV2001** (N=582) have been assessed at time of conditional MA. Since then, no additional subjects have been enrolled in these trials. There were no relevant differences in baseline or demographic characteristics between the vaccine groups, including placebo, in any of the studies/cohorts. Analyses presented in the variation include data of selected groups of each study.

In **COV3009**, in total 31,300 participants were randomized and vaccinated in in the 'Ad26 $5x10^{10}$, Ad26 $5x10^{10}$' arm (N=15,708) or to the 'placebo, placebo' arm (N=15,592) in the double-blind phase. See efficacy assessment for further details. Whether the absence of differences are also applicable to the immunogenicity data set analyzed is not mentioned. In the current application, immunogenicity data of study COV3009 are available for a limited number subjects of the immunogenicity subset. It is expected that baseline or demographic characteristics for the immunogenicity subset will be presented when immunogenicity data are available for the whole immunogenicity subset.

In the **Mix and Match study**, baseline characteristics of participants in the 3 concerned groups (booster vaccination with COVID-19 vaccine Janssen after primary vaccination with the same vaccine, Spikevax or Comirnaty) were similar: median age of approximately 50 years; at least 30% of each gender; and majority are white. The mean interval between primary and booster vaccination was 17.7 weeks, 19.3 weeks and 20.6 weeks in the groups who were primary vaccinated with COVID-19 vaccine Janssen, Spikevax and Comirnaty, respectively.

Results

Immune responses following 1 single dose of the COVID-19 Vaccine Janssen

Original SARS-CoV-2 strain

The main data on the durability of neutralizing and binding Ab responses against the original SARS-CoV-2 strain up to at least 6 months after 1 single dose of the COVID-19 Vaccine Janssen (5×10^{10} vp dose level) are available from studies **COV2001** (Group 5, up to 6 months) and **COV1001** (Group 2 for both Cohort 1a and Cohort 3, up to 8-9 months).
COV2001 nAb data are available for 33 vaccinees, including 20 subjects of 18-55 yoa and 13 of ≥65 yoa. Binding Ab results are available for 73 subjects, including 44 vaccinees of 18-55 yoa and 29 of ≥65 yoa. **COV1001** nAb data are available for 41 subjects, including 22 vaccinees of 18-55 yoa and 19 of ≥65 yoa. Binding Ab results are available for 135 subjects, including 68 vaccinees of 18-55 yoa and 67 of ≥65 yoa.

Data up to 6 months are also available from 17 subjects of **COV1001** Cohort 2a. Humoral and cellular immune responses up to 8 months post-vaccination are also available for 5 subjects of COV1001 Cohort 1b.

Based on the main data from both studies **COV1001** and **COV2001**, which is limited, the humoral immune responses induced following the administration of 1 single dose of the COVID-19 Vaccine Janssen appears to be sustained up to at least 6 months. There is no clear decrease over time. A minor, and not systematic, trend for decreased Ab levels is observed at the later timepoints (6 or 8-9 months post-vaccination) when compared to earlier timepoints (1 or 2 months post-vaccination). 95% CIs always overlapped. Based on available data, it is not possible to conclude if these observations suggest the start of a waning of humoral immune responses or are only due to variability inherent to the limited sample.
Limited data from Cohort 1b and Cohort 2a of study COV1001 also suggest stable (or even increase of) immune responses over time post-vaccination up to 6 months.

It is not known if the Ab levels will decrease or will be maintained after 6-9 months post-vaccination with 1 single dose of the COVID-19 Vaccine Janssen, and if this will impact the clinical protection.

Of note, the T cell responses appear to be sustained over time (based on very limited number of subjects of Cohort 1b).

SARS-CoV-2 Variants

Few samples from 18-55 yoa adults in Cohort 1a (n=6) and Cohort 1b (n=4) of **COV1001** were tested for the presence of nAb against VOC.

Overall, data suggest that the nAb induced by a single dose of COVID-19 Vaccine Janssen have less neutralizing capacity against the Delta and the Beta variants compared to the original strain and the Alpha strain. nAb could still be detectable at 8 months post-vaccination, but not in all samples.

As for the parental strain, it is not known how the Ab titers will evolve over time after 8 months.

Immune responses following 2 doses of the COVID-19 Vaccine Janssen

Original SARS-CoV-2 strain

Data available

Data on homologous booster vaccination 2, 3 or 6 months after dose 1 (with the dose level of 5×10^{10} vp or 1.25×10^{10} vp) are available from studies **COV1001** (Cohort 1a and Cohort 3, 2 and 3 month-interval between doses, respectively; Cohort 2a, 6 month-interval between doses), **COV1002** (Cohorts 1 and 2, 3 and 2 month-interval between doses, respectively), **COV2001** (Groups 1 and 9, 2 and 3 month-interval between doses, respectively; Group 5, booster dose (second dose) of 1.25×10^{10} vp) and **COV3009** (2 month-interval between doses).

In **COV1001**, nAb results up to 6 months post-dose 2, when given at 2 or 3 months post-dose 1, are available for 24 participants of 18-55 yoa (Cohort 1a) and 21 participants of 65 yoa or older (Cohort 3). Binding Ab results post-dose 2 are available for 70 participants of Cohort 1a and 71 participants of Cohort 3. nAb and binding Ab results are also available for 17 subjects of 18-55 yoa (Cohort 2a) up to 1 month post-dose 2 that was given 6 months after the first dose.

nAb and binding Ab results are available for 43 younger adults and for 48 older adults of study **COV1002** up to 1 month post-dose 2.

Post-dose 2 immunogenicity data (up to 1 month post-dose 2) of study **COV2001** are available for 75 (45 subjects of 18-55 yoa and 30 subjects of ≥65 yoa) and 127 (79 subjects of 18-55 yoa and 48 subjects of ≥65 yoa) subjects for nAb and binding Ab, respectively. Among the 75 participants for whom nAb data are available 38 and 37 received the booster dose (second dose) 56 or 84 days after the first dose, respectively. Among the 127 participants for whom binding Ab data are available, 80 and 47 received the booster dose (second dose) 56 or 84 days after the first dose, respectively. Binding Ab results at 6 months post-dose 1 were also available for 50 and 27 younger adult and older adult subjects, respectively.
Anamnestic responses after antigen presentation at a dose level of 1.25×10^{10} vp were evaluated in the participants of Group 5 of study COV2001. Binding Ab responses post-boost up to 1 month are available for 71 subjects, including 43 vaccinees of 18-55 yoa and 28 of ≥65 yoa.

Finally, post-dose 2 binding Ab data (up to 14 days post-dose 2) of study **COV3009** are available for 17 and 15 vaccinated subjects of 18-59 yoa, without and with comorbidities respectively, and for 24 and 22 vaccinated subjects of 60+ yoa, without and with comorbidities respectively.

Humoral Immune responses up to 1 month post-dose 2

Overall, a second vaccine dose of Ad26.COV2.S, given at 2, 3 or 6 months post-primary vaccination, induces an increase in nAb and binding Ab titers, when compared to pre-boost values, both in younger and older adults. GMTs increase, ranging from 1.5 to 4.4 fold for nAb and from 2.5 to 5.8 fold for binding Ab, between pre-boost and 1 month post-boost.

nAb data of study **COV2001** suggest a slightly added value of giving the booster dose (second dose) 3 months, instead of 2 months, after the first dose. GMT tend to be higher at 1 month post-boost when given at 3 months versus 2 months post-primary vaccination. This was true for both the younger and the older adults.

Limited **COV1001** data obtained when the booster dose (second dose) is given at 6 months post-dose 1 show an increase in nAb. GMT at 7 days post-boost are higher than those observed in study COV2001, for the same age group.

As for the nAb results, **binding Ab** data of study **COV2001** suggest a slightly added value of giving the booster dose (second dose) 3 months, instead of 2 months, after the first dose. This was true for both the younger and the older adults. Of note, when the booster dose (second dose) was given 2 months after the first dose, a similar GMT fold-increase pre- to 14 days post- dose 2 was observed in study **COV3009** when compared to study COV2001.

The available data are not suitable to conclude on potential differences between the 2- and 3-months interval between primary and booster dose, as GMTs were not systematically in the same range when same populations (age range, comorbidity status) vaccinated with the same time interval between doses, were compared across studies. Responses were also variable between age subgroups when the booster dose (second dose) was given at the same interval post-primary vaccination.

When the booster dose is given 6 months post-dose 1, GMTs observed 14 days after vaccination in younger adults were higher than those observed when the boost is given 2 or 3 months post-dose 1.

Overall, although there is a trend for higher Ab GMTs post-boost with longer interval between doses, it is considered that no conclusion can be drawn since these observations are based on too limited data.

In addition, whether the differences observed post-boost GMTs between age groups in study COV2001, and across studies, is due to the presence of comorbidities, higher or lower Ab GMT values pre-dose 2 or to the limited sample size cannot be concluded. These should be confirmed when the complete data of studies COV3009 and COV2008 will be available.

Humoral immune responses up to 6 to 8 month post-dose 2

Both **nAb** and **binding Ab** results of studies **COV1001** and **COV2001** indicate that the Ab levels reached post-dose 2, when given at 2 or 3 months interval between doses, decline over time. A two-fold decrease was observed from 1 to 4 or 6 months post-dose 2. GMTs at 4 or 6 months post-dose 2 were still higher than at 1 month post-dose 1.

Functional Antibody Characterization up to 1 month post-dose 2

The proportion of samples with detectable **functional Ab** (i.e. other than nAb and with a suggested role in viral clearance in vivo), as well as the median of response, tend to increase from pre- to post-dose 2 in both younger (Cohort 1a, n=72) and older (Cohort 3, n=73) adults of study **COV1001**. Phagocytic score GMs (95% CI) observed 1 month post-dose 2 were similar for both cohorts, i.e. whatever the age of the participants and the time interval between doses (2 or 3 months).

Cellular immune response up to 1 month post-dose 2

Specific **CD4** and **CD8** T cell responses were analyzed for 39 and 40 participants of **COV1001** Cohort 1a and Cohort 3, respectively. Data observed on this limited sample size indicates that the second vaccine dose does not induce an increase in the CD4 and CD8 Th1 cell responses in younger adults. The proportion of older subjects with detectable CD4 or CD8 Th1 responses was slightly increased, but the median of response in positive samples remained similar as pre-dose 2.

SARS-CoV-2 Variants

Very limited humoral data are available for the Alpha and Beta variants (n=6) 14 days post-dose 2, given 2 months post-dose 1. Ab titers against variants increased following the second vaccine dose. nAb titers against the Alpha variant following the second vaccine dose reached a comparable level as observed for the Victoria strain following the first vaccine dose. nAb titers post-dose 2 against the Beta variant remained low. There are no data for the Delta variant, which is currently the dominant circulating variant in EU.

The neutralizing capacity of the Ab induced by a booster dose, given 6 months after the first dose, was also measured in the samples of 17 subjects included in the Cohort 2a of the **COV1001** study. nAb titers to the Gamma, Delta, and Lambda variants were measured by a developed, non-qualified, psVNA (JBDA). Data were also obtained for the Beta variant on the same samples with a partially validated psVNA (Monogram). It is likely that both the psVNAs lack of sensitivity. Measurement with a test with adequate performance, and correlated with the wtVNA, would have been preferred.

Overall, for all the VOCs, an increase of Ab titers is observed post-boost, as early as 7 days after the boost. nAb levels observed 1 month post-boost for the variants are lower than for the parental strain. However, post-boost Ab levels for the variants appear to be similar or higher than pre-boost Ab levels for the parental strain. Noteworthy, the pre-boost Ab level for the parental strain was low, and the GMT observed at 1 month post-primary vaccination was <LOD with the psVNA (JBDA), which add limitation for interpreting the results. The Ab levels 1 month post-dose 1 are not available, with the exception of Ab levels for the Beta variant measured with the psVNA of Monogram.

Limitations for interpreting the data following 2 doses of the COVID-19 Vaccine Janssen

There are no results from a dedicated booster study COV2008, the study is ongoing.

The humoral immune responses elicited by a booster dose were investigated before immunogenicity started to wane.

Results are from different studies, always with limited sample size, in particular for nAb (even no data from study COV3009).

Most of the results are for the original Victoria strain. Limited data are available for the variants of concern. There are no Ab data for the Delta variant when the booster dose (second dose) is given at 2 months post-dose 1. Only limited data are available when the booster dose (second dose) is given with a 6 month-interval and several limitations have to be considered. First of all, data are generated by a developed (non-qualified) psVNA that seems to lack sensitivity. In addition, immune responses for these subjects do not follow the same kinetics up to 6 months post-dose 1 compared to other studies.

A post-hoc non-inferiority analysis was performed on 17 subjects that received a boost 6 months after the primary vaccination. Since pre-boost Ab levels were not declined compared to 1 month post-dose 1, this analysis is not considered relevant.

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

COV2001 is the only study that allows comparison of different time-interval (2 vs 3 months) between groups of the same age range. Data for the boost at 6 months post-primary vaccination are limited. Overall, data are too limited to firmly conclude on the optimal time interval between doses.

CMI data are very limited and from 1 study only.

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

There are no established immune correlate of protection, although it is recognized that Ab are associated with protection.

Immune responses following 1 dose of the COVID-19 Vaccine Janssen in subjects primary vaccinated with mRNA vaccines

Overall, data of the **Mix-and-Match study (DMID 21-0012)** indicate that neutralizing and binding Ab levels increase after homologous and heterologous (primary vaccination with Comirnaty or Spikevax) booster vaccination with COVID-19 vaccine Janssen. Although the study was not designed to make comparisons across vaccines and strategies, the data indicate the homologous regimen with COVID-19 vaccine Janssen induces the lowest Ab response. Heterologous boosting with COVID-19 vaccine Janssen after primary vaccination with an mRNA vaccine induces lower Ab levels compared to homologous boosting with an mRNA vaccine on Day 15. However, by Day 29, nAb titers are roughly similar in those groups, as nAb titers tend to further increase after heterologous boosting with COVID-19 vaccine Janssen, while nAb titers decrease by Day 29 after homologous mRNA vaccination.
These data are in line with the publication of Sablerolles et al. (not peer reviewed) describing results of the SWITCH trial in The Netherlands. In this study, healthcare workers who received COVID-19 vaccine Janssen as primary vaccination, were administered a homologous boost or heterologous boost with an

mRNA vaccine (Comirnaty or Spikevax) with an interval of approximately 3 months. On Day 29, Ab levels after a heterologous booster were increased to higher levels when compared to homologous booster with COVID-19 Vaccine Janssen. Limited data of an observational study in 55 subjects also support these finding, as they show an expanded breath of humoral and cellular immunity after heterologous JJ/BNT vaccination vs. homologous JJ vaccination (Huat NKK et al.). Results on heterologous priming with the other adenovirus based vaccine, Vaxzevria, support the above findings. The COM-COV trial, published by Liu et al., indicates that heterologous priming with one dose of Comirnaty followed by one dose of Vaxzevria induces much lower Ab responses compared to homologous priming with Comirnaty. Finally, the MAH shared non-peer reviewed results, including preliminary data of the study COV2008, with the Rapporteur (Tan et al.). Individuals primary vaccinated with Comirnaty, who received a homologous booster dose with Comirnaty after 6 months, had much higher Ab levels (neutralizing and binding) two weeks after the booster compared to individuals who received a heterologous booster with Ad26.COV2.S. However, at 4 weeks after a booster, Ab titers decreased in the Comirnaty booster group while Ab titers further increased in the Ad26.COV2.S booster group, resulting in similar Ab levels in both groups. Of note, the number of subjects included are very limited, in particular at week 4. These findings seem to be in line with data of the COV-BOOST study, published very recently (Munro et al.). COV-BOOST study is a multicenter, randomized, controlled, phase 2 trial of a third dose booster vaccination against COVID-19. Participants enrolled were 30 years and older, and were at least 70 days post two doses of Vaxzevria or at least 84 days post two doses of Comirnaty primary COVID-19 immunization course, with no history of laboratory-confirmed SARS-CoV-2 infection. Within each site group, participants were randomly assigned to an experimental vaccine or control, including Comirnaty and COVID-19 vaccine Janssen. Roughly similar nAb titers are measured 28 days after a boost with Comrinaty or COVID-19 vaccine Janssen, 10-12 weeks after primary vaccination with Comirnaty, both against Wild-Type SARS-CoV-2 and the Delta variant. Binding Ab titers against the WT virus are higher after homologous boosting with Comirnaty. Kinetics of the binding Ab response differ between booster vaccines, with high Ab titers being already observed as soon as 7 days post-boost with Comirnaty, whereas an increase of Ab titers is observed between day 7 and day 28 post-boost with COVID-19 vaccine Janssen.

The clinical relevance of the increase in neutralizing and binding Ab titers after a booster with COVID-19 vaccine Janssen is unknown. CMI data are not available yet.

As only short term data are available on heterologous boosting, long-term protection and immunological memory are currently unknown.

CONCLUSION

Based on limited data, it can be concluded that, after a single dose of COVID-19 Vaccine Janssen, there is no clear evidence of waning of immunity up to at least 6 months. It is not known how the immune responses will evolve over time and the impact on clinical protection.

Most of the results are for the original Victoria strain. A booster dose (second dose) of COVID-19 Vaccine Janssen, given at 2, 3 or 6 months post-primary vaccination, induces an increase in both neutralizing and binding Ab, when compared to pre-boost values, in both young and older adults. GMTs increase, ranging from 1.5 to 4.4 fold for nAb and from 2.5 to 5.8 fold for binding Ab, between pre-boost and 1 month post-boost. Functional Ab against the original strain, other than nAb and with a suggested role in viral clearance in vivo, tend to increase post-dose 2. CMI data are limited and do not suggest an increase in the CD4 and CD8 Th1 responses with a booster dose (second dose).

Limited data post-dose 2, when given at 2 months after the first dose, are available for the VOC (Alpha and Beta). The data suggest an increase in nAb. nAb levels observed 1 month post-boost for the variants are lower than for the parental strain at the same timepoint. There are no Ab data for the Delta variant when the booster dose (second dose) is given at 2 months post-dose 1. Only limited data are available when the booster dose (second dose) is given with a 6 month-interval (for the Beta, Gamma, Delta, Lambda variants), with several limitations for interpreting the data.

There are no Ab data in elderly who received a boost at 6 months post-primary vaccination.

Data over a longer period of time than 1 month post-dose 2 are limited. A 2-fold decline of Ab titers is observed at 4-6 months post-dose 2. Whether Ab titers will continue to decline over time is not known.

Data are too limited to conclude on the optimal time interval between doses.

Data indicate the homologous regimen with COVID-19 vaccine Janssen induces lower Ab responses compared to heterologous boosting with an mRNA vaccine.
Current evidence suggest that heterologous boosting with COVID-19 vaccine Janssen after primary vaccination with an mRNA vaccine induces lower Ab levels compared to homologous boosting with an mRNA vaccine after 14-days, while after 1 month, neutralizing antibody titers are roughly similar between both regimens.

There are no established immune correlate of protection, although it is recognized that Ab are associated with protection.

Please, refer to the published EMA and ECDC recommendation on heterologous vaccination courses against COVID-19 and the SmPC for additional information.

4. Clinical Efficacy aspects

In the context of this booster dose (second dose) variation, key data that support the variation for the booster dose (second dose) variation are the immunogenicity and safety data. Efficacy data is supportive of the variation.

Preliminary efficacy results up to the end of the double-blind phase, which corresponds to the final analyses, have been provided for the Pivotal Phase 3 study COV3001. COV3001 (ENSEMBLE1) is the pivotal efficacy trial which assessed a single dose schedule and supported the MA. The results are over an approximately 4 months median FU period. Only TLRs are available for this final analysis of the double-blind phase.

Preliminary efficacy results up to the end of the double-blind phase have been provided also for the Pivotal Phase 3 study COV3009. COV3009 (ENSEMBLE2) is the pivotal efficacy trial which assesses a two dose schedule. The data correspond to the primary analysis of the trial, which is also the final analysis of the double blind phase. Only Top line results (TLRs) are available, and genomic analyses are incomplete (68% sequencing).

4.1. Design

Design of study COV3001

The design of COV3001 was assessed as part of the conditional MA.

COV3001 is a randomized, double-blind, placebo-controlled, Phase 3 study performed in adults ≥18 years of age. The study was conducted in the US, several Latin American countries (Argentina, Brazil, Chile, Peru, Mexico, Colombia), and South Africa. Participants were randomized in parallel in a 1:1 ratio to receive Ad26.COV2.S at a dose level of $5x10^{10}$ vp or placebo intramuscularly. 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. Randomization was stratified by site, age group (≥18-<60 yoa vs ≥60 yoa), and absence/presence of comorbidities that are or might be associated with an increased risk of progression to severe COVID-19.

Following Emergency Use Authorization (EUA) in the US (on February 27, 2021), the Ad26.COV2.S vaccine was offered to participants who initially received placebo. Therefore, participants and investigators were unblinded. The crossover resulted in loss of placebo-controlled follow up. All participants were 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 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) harmonized 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 case definition of moderate COVID-19 includes two sets of criteria using a combination of symptoms and signs. The MAH used a complex composite definition of moderate COVID-19, of unclear added value. 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.

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 were adjudicated in a blinded manner by the Clinical Severity Adjudication Committee (CSAC).

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. 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 harmonized case definition.

Design of study COV3009

COV3009 is a randomized, double-blind, placebo-controlled phase 3 study. The design and endpoints are similar to the COV3001 trial.

The study was conducted in Europe and the US mainly, which is different from COV3001 that included no European site and was mainly in the US and South America.

Participants were randomized in a 1:1 ratio to receive 2 doses of Ad26.COV2.S at a dose level of $5x10^{10}$ vp 56 days apart or placebo intramuscularly.

The sample size calculation for this trial was driven by the primary analysis which aimed to demonstrate VE>30% with the per protocol population. The definition of events was predefined as first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 in the PP population at least 14 days after the 2nd vaccination (Day 71) with study vaccine. The target sample size for the study was approximately 30,000 participants (≈15.000 patients per group) and 104 overall events for the per protocol population.

No interim analysis was planned to prematurely stop the trial for overwhelming efficacy.

A graphical approach (Bretz et al, 2009) was planned to handle multiplicity along the primary endpoint and the secondary confirmatory endpoints. The primary endpoint, and the 3 following secondary endpoints covered by the multiplicity rules were significant: burden of disease endpoint, all SARS-CoV-2 infections, and severe events; the asymptomatic infections and the need for medical intervention were not, therefore, any additional endpoint is not further covered by the multiplicity strategy.

For both studies, participants are included in the analysis of the double-blind phase but are censored at the day of unblinding, the day of administration of another authorized/approved COVID-19 vaccine (if any, including Ad26.COV2.S if received outside of the study), the date of study discontinuation or the last available date (datalock point), whichever occurred first.

Events that occurred after receipt of another COVID-19 vaccine (including the Ad26.COV2.S if received outside of the study) are tabulated separately. Placebo recipients crossed-over to the Janssen COVID-19 vaccine (as part of the study) were evaluated in the placebo group for the time they were exposed under placebo injection and evaluated in the vaccine group for the time post Janssen COVID-19 vaccination.

4.2. Results

Phase 3 Study COV3001

Criteria for analysis and subjects disposition

The primary analysis of COV3001 was performed when the 2-month median follow-up timepoint was reached (database cut-off date: 22 January 2021). The primary analyses results are discussed in the conditional MA report. The MAH now presents the final analysis results of the double blind phase of the pivotal COV3001 trial which is assessing a single dose schedule. The cut off date is July 9, 2021 for this analysis with a median follow-up of approximately 4 months.

FAS:

In the final analysis results of the double blind phase, 43,788 participants were vaccinated (21,898 and 21,890 in the Ad26.COV2.S and placebo group). This constitutes the Full Analysis Set (FAS).

Unblinding and premature termination:

Study participants who became eligible to receive an authorized/licensed COVID-19 vaccine according to local recommendation could request to be individually unblinded (Protocol Amendment 3). Following EUA approval, all participants were systematically unblinded (Protocol Amendment 4). Participants were encouraged to continue to be followed as part of the open label phase.

Up to the cut-off date of the final analysis of the double-blind phase (9 July 2021), most participants in the FAS (94.7%) were actually unblinded (95.0% vs 94.4% in the Ad26.COV2.S and placebo group, respectively).

A slightly higher proportion of subjects terminated the double blind phase prematurely in the placebo group (8.8%) vs the active group (5.4%), and the main reason for discontinuation was receival of another vaccine, followed by withdrawal and lost to follow up.

PP set:

The primary and final analyses of efficacy was based on the Per-protocol Efficacy (PP) population. Of the participants in the FAS, 39,185 (19,577 and 19,608 in the Ad26.COV2.S and placebo group) were included in the PP set.). Baseline seropositivity for SARS-CoV-2 was the main reason for elimination from the PP set. Other reasons were being PCR positive at baseline or protocol deviations. Reasons for elimination from the PP were balanced across groups.

Follow up period:

The median follow up after double blind vaccination was 4 months (123 days in the FAS and 121 days [min-max]: 1-284 days in the PP). Overall, 22.8% of the participants (23.5% vs. 22.2% in the active vs placebo group) had a follow up of at least 6 months (defined as 24 weeks) in the PP. The median follow up was 122 days and 120 days in the active vs the placebo group (PP).

The study introduced the possibility to cross-over to the Janssen vaccine for the placebo subjects, so all subjects were unblinded at a schedule study visit after EUA, which explains the short FU period.

The length of follow up varied across countries, and according to baseline characteristics. This is because: (i) Enrolment started at different time across countries (first in the US, with other countries following later at various periods), (ii) Safety pauses occurred at different time across countries, (iii) Per study design, elderly participants and participants with comorbidities were enrolled later, (iv) Calendar time at unblinding of participants differed across countries. This resulted in differences in the person-years of follow-up for case accrual between subgroups. This has an important impact on the time to follow-up in some subgroups, such as the elderly. There are also differences in terms of vaccination periods across countries and subgroups. This could also lead to biased efficacy estimates in the subgroups, also given different variant pattern across countries and time calendar.

Demographics and baseline characteristics

The study was conducted in the United States (44.1% of the FAS), various countries of Latin America (40.9% of the FAS, from Brazil, Colombia, Argentina, Peru, Chile and Mexico), and South Africa (15.0% of the FAS). There was no European site in this study.

In the FAS, 4,275 (9.8%) of participants were SARS-CoV-2 seropositive at baseline.

The median age of individuals was 52.0 years (range: 18-100), 33.5% of the participants were 60 yoa or more, and 42.0% has comorbidities putting them at risk of severe COVID19 (FAS).

The proportion of participants ≥60 years was 35% (in the PP) and the proportion of participants ≥65 years was 20%. The proportion of participants ≥75 years was however limited (4% in the PP).

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% (PP), 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 MAH is planning an immunogenicity study in immunocompromised individuals in the PM period.

Baseline characteristics were well balanced across arms, overall and within regions.

Variants circulation

Of the 2056cases (including mild and asymptomatic cases) that occurred during the double-blind phase of the study as of Day 1, 1836 (89%) have sequencing data available.

The final CSR will include sequencing data from all available cases in the double blind phase up to the cut-off date 9 July 2021.

During the observation period, new SARS-CoV-2 variants emerged, with important variations across countries and over time.

There was a diversity of variants, with no dominating variant over the study period. Overall, cases included the reference sequence (14%) (mainly in the US), the Gamma/P1 (13%), and the Zeta/P2 (11%), Beta/B.1.351 (8%), Mu/B.1.621 (7%), Lambda/C.37 (6%), and other variants, such as Epsilon (California, B.1.427/429). There were very limited cases of Alpha/B.1.1.7 (3%) and Delta/B.1.617.2 (2%). In the PP, the circulating variants over the period were the same: reference sequence (9%), the Gamma/P1 (12%), and the Zeta/P2 (8%), Beta/B.1.351 (6%), Mu/B.1.621 (6%), Lambda/C.37 (6%). There were very limited cases of Alpha (2%) and Delta (1%) (*Figure 17*).

All over the trial COV3001, there is a high proportion of the other mutations category (30%),which includes all variants that were not labelled as Reference (Wuhan+D614G), VOC (Alpha, Beta, Gamma, or Delta), VOI (Lambda, or Mu), or any other variant with significant presence in any of the participating countries that might have been classified as VOI previously (such as P.2/Zeta in Brazil, or P.3/Theta in Philippines), and without E484K, at the time of the analysis.

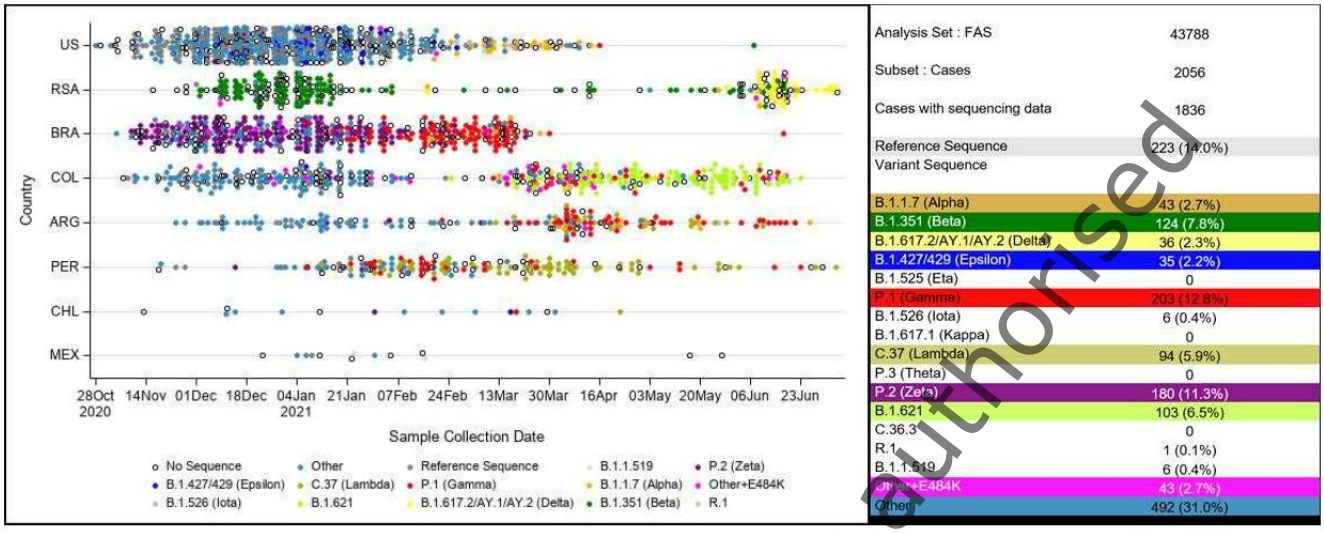
There were 258 sequences classified as "Other" in study COV3001. In study COV3009, 47 of the available sequences were classified as "Other".

The MAH explained that he variation of the "Other" category between countries and between studies (COV3001 versus COV3009) is likely due to a different epidemiology of those strains versus the different VOC/VOIs. The gradually decreasing numbers in the "Other" category could be explained by a lower transmissibility and lower resistance to neutralization of these strains leading to a replacement by the circulating VOC/VOI.

The variants evolved a lot over time. At the beginning of the period, the referent variant was predominant (mainly in the US), as well as the Beta/B.1.351 (in SA), and the Zeta/P.2 (in Brazil). These were the main variants, for the cases in the primary analysis supporting MA.

The reference sequence disappeared after 2-3 months, and several other variants are observed, such as the Gamma/P1 (in Brazil), and the Lambda/C37 (in Peru). At the end of the FU period cases of Mu/B.1.621 (in Colombia) and Delta/B.1.617.2 variants (in SA) were observed.

Figure 17: Distribution of Cases by Variant and by Country



Co-primary and Key Secondary Endpoints

The results for the primary and key secondary endpoints are presented in *Table 10* for events with onset at least 14 days after vaccination and for events with onset at least 28 days after vaccination (co-primary endpoints).

The point estimates of efficacy against symptomatic disease were lower at the final versus the primary analysis, while point estimates of efficacy against severe disease were similar at the primary and the final analysis.

Events with an onset at least 14 days after vaccination:

In total, 484 vs 1067 cases of moderate-to-severe COVID-19 (primary endpoint) occurred in the active vs the placebo group. For the primary endpoint moderate-to-severe COVID-19, which corresponds to symptomatic COVID-19 (any severity), efficacy was 56.3% (95% CI: 51.30; 60.84). At the primary analysis, the point estimate was 66.9% (Adjusted 95% CI: 59.03; 73.40). Point estimates were lower at the final vs. the primary analysis, but 95% CI overlap. There were only 26 additional mild cases, as the primary endpoint captured most mild cases.

The number of cases was large, making the estimates robust, even for severe COVID-19 cases. At the final analysis, the point estimate of VE against severe disease was 73.3% (Adjusted 95% CI: 63.94; 80.49), while at the primary analysis, the point estimate of VE against severe disease was 76.7% (Adjusted 95% CI: 54.56; 89.09).

Efficacy estimates for COVID-19 requiring medical intervention, which in practice corresponds to COVID-19 related hospitalization (see MAA assessment report) was 76.1% (95% CI: 56.86; 87.67). For COVID-19 related death efficacy was 84.5% (95% CI: 47.30; 97.06). The point estimates were thus consistent with those for severe disease. For COVID-19 related deaths, this was based on 3 vs. 19 events in respective groups.

Events at least 28 days after vaccination:

There were 433 vs 883 cases of moderate-to-severe COVID-19. For the primary endpoint moderate-to-severe COVID-19, (ie. symptomatic COVID-19 of any severity), efficacy was 52.9% (95% CI: 47.06; 58.08). The point estimate is lower compared to what was observed at MA in the primary analysis after a 2 months median FU period. At that time, efficacy was 66.1% (95% CI: 55.01; 74.80). There were only 22 additional mild cases, as the primary endpoint captured most mild cases.

For severe COVID-19, the point estimate of efficacy was 75% (74.6% [95% CI: 64.70; 82.06]). It was 85% at the time of the primary analysis, that is over a 2 months median FU period (85.4% [95% CI: 54.15; 96.90]). For the hospitalized cases, the point estimate was 76%.

Table 10: Summary of Vaccine Efficacy (Primary and Final Analysis) Against COVID-19 With Onset at Least 14 And 28 Days After Vaccination, Per Protocol Set (Study VAC31518COV3001)

	Primary Analysis[f] - VE ([Adjusted] 95% CI)		Final Analysis[g] - VE ([Adjusted] 95% CI)	
	At least 14 days	At least 28 days	At least 14 days	At least 28 days
Analysis set: Per protocol set Risk set[a]				
Primary endpoint				
Moderate and severe/critical COVID-19	66.9% (59.03; 73.40)	66.1% (55.01; 74.80)	56.3% (51.30; 60.84)	52.9% (47.06; 58.08)
Age 18-59 years	63.7% (53.87; 71.58)	66.1% (53.30; 75.77)	56.6% (51.00; 61.67)	54.3% (47.95; 59.97)
Age ≥60 years	76.3% (61.58; 86.04)	66.2% (36.74; 82.99)	55.0% (42.87; 64.73)	46.6% (30.74; 58.99)
Age ≥65years	82.4% (63.90; 92.38)	74.0% (34.40; 91.35)	63.8% (48.88; 74.81)	58.5% (39.25; 72.09)
Age ≥75 years	100.0% (45.90; 100.0)	0 vs 3 (VE not calculated)	48.3% (-26.13; 80.05)	22.3% (-112.78; 72.06)
Secondary endpoints				
All SARS-CoV-2 infections	--	67.2% (56.86; 75.26)	--	41.7% (36.32; 46.71)
Any symptomatic COVID-19 severity	66.9% (59.07; 73.37)	66.5% (55.50; 75.05)	55.9% (50.95; 60.46)	52.4% (46.63; 57.64)
Mild			29.4% (-64.57; 70.66)	19.9% (-102.28; 69.00)
Moderate	64.8% (55.75; 72.21)	62.0% (48.68; 72.21)	52.1% (46.11; 57.40)	47.2% (40.21; 53.51)
Severe/critical	76.7% (54.56; 89.09)	85.4% (54.15; 96.90)	73.3% (63.94; 80.49)	74.6% (64.70; 82.06)
Asymptomatic SARS-CoV-2 infections[c]	--	74.0% (27.89; 92.40)	--	28.9% (19.99; 36.78)
All symptomatic COVID-19 (BOD)[b] molecularly confirmed	68.1% (60.26; 74.32)	69.0% (56.68; 77.64)	57.2% (52.13; 61.66)	54.3% (48.55; 59.42)
Req. Medical intervention[d]	75.0% (-25.28; 97.41)	0 vs 5 (VE not calculated)	76.1% (56.86; 87.67)	75.6% (54.26; 88.00)
All cause mortality	80.0% (29.36; 96.29)	75.0% (-25.15; 97.42)	58.5% (27.61; 77.08)	49.9% (10.63; 72.79)
COVID-19 related mortality[e]	0 vs 5* (VE not calculated)	0 vs 3* (VE not calculated)	84.5% (47.30; 97.06)	82.8% (40.49; 96.77)
Supplementary Endpoints				
US FDA Harmonized COVID-19 cases	67.2% (59.32; 73.67)	66.7% (56.63; 75.23)	55.6% (50.52; 60.16)	52.0% (46.18; 57.32)

* COVID-19 related mortality for the primary analysis is based on the onset of the AE and per Janssen WHO clinical assessment within the FAS.
The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.
If fewer than 6 cases are observed for an endpoint then the VE will not be shown.

a. The risk set are all subjects of the PP Set excluding subjects that had a positive PCR test between day 1 and day 14 or day 28.
b. BOD: Burden of Disease is a weighted version of the mild, moderate, and severe/critical vaccine efficacies.
c. **Primary analysis**: asymptomatic/undetected SARS-CoV-2 infection was defined as a participant who did not fulfil the criteria for suspected COVID-19 based on signs and symptoms but had a positive RT-PCR test or developed positive serology (with defined symptoms but without a positive RT-PCR test). This was a preliminary analysis based on limited availability of data. 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. **Final Analysis**: asymptomatic SARS-CoV-2 infection was defined as a participant who did not fulfil the criteria for suspected COVID-19 based on signs and symptoms which would classify them as mild, moderate, or severe by the protocol definitions but who had a positive RT-PCR test or developed positive serology. Potential symptomatic cases that were identified by either a positive RT-PCR test or N protein specific SARS-CoV-2 seroconversion were all to be examined by the CSAC for the presence of any signs or symptoms and if found, determined if they would still be classified as asymptomatic COVID-19.
d. **Primary Analysis**: Medical intervention is defined as hospitalization, ICU admission, mechanical ventilation, ECMO, linked to objective measures as decreased oxygenation, X-ray or CT findings, as reported on the MRU form, completed by the investigator. **Final Analysis**: Molecularly confirmed COVID-19 cases requiring medical intervention including hospitalization, ICU admission, mechanical ventilation and ECMO were based on objective findings such as decreased oxygenation, X-ray, CT findings, use of supportive medications or clinical course following adjudication by the CSAC.
e. **Primary Analysis**: Positive RT-PCR and COVID-19 related. **Final Analysis**: A fatality is COVID-19 related if it is COVID-related according to the CSAC or was a fatal AE that was COVID-19 related after the onset of a COVID-19 episode with at least 1 documented RT-PCR.
f. Cut-off date: 22 January 2021.
g. Cut-off date: 09 July 2021.

Sources: TEFSUM01A, TEFSUM01C, GEFPE02AS1, GEFPE02CS1

Table 11: Summary of Vaccine Efficacy Against COVID-19 With Onset at Least 14 Days After Vaccination; Per Protocol Set Final Analysis of Double-Blind Phase (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		(19577)		(19608)			
Risk set[a]		(19400)		(19398)			
Primary endpoint							
Moderate and severe/critical COVID-19	484	6685.60	1067	6440.18	56.3%	(51.30; 60.84)	
Age 18-59 years	381	4682.12	847	4514.15	56.6%	(51.00; 61.67)	
Age >=60 years	103	2003.48	220	1926.03	55.0%	(42.87; 64.73)	
Secondary endpoints							
Any symptomatic COVID-19 severity	495	6683.78	1082	6437.40	55.9%	(50.95; 60.46)	
Mild	11	6683.78	15	6437.40	29.4%	(-64.57; 70.66)	
Moderate	429	6685.60	862	6440.18	52.1%	(46.11; 57.40)	
Severe/ critical	56	6774.58	205	6625.15	73.3%	(63.94; 80.49)	
All symptomatic COVID-19 (BOD)[b] molecularly confirmed	495	6683.78	1082	6437.40	57.2%	(52.13; 61.66)	
Req. Medical intervention	18	6783.90	74	6656.73	76.1%		(56.86; 87.67)
All cause mortality	19	6786.99	45	6669.34	58.5%	(27.61; 77.08)	
COVID-19 related deaths[c]	3	6786.85	19	6668.43	84.5%	(47.30; 97.06)	
Supplementary Endpoints							
US FDA Harmonized COVID-19 cases	492	6684.70	1067	6440.45	55.6%	(50.52; 60.16)	

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI

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.
[c]A fatality is covid-19 related if it is covid-related according to the adjudication committee or it has a fatal adverse event that is covid-19 related after the onset of a covid-19 episode with at least 1 documented PCR
NE: Not Evaluable

[TEFSUM01A.RTF] [VAC31518\VAC31518COV3001\DBR_IA_FINAL_DB\RE_IA_FINAL_DB\PROD\TEFSUM01A.SAS] 29JUL2021, 11:00

Table 12: Summary of Vaccine Efficacy Against COVID-19 With Onset at Least 28 Days After Vaccination; Per Protocol Set Final Analysis of Double-Blind Phase (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		(19577)		(19608)			
Risk set[a]		(19113)		(18924)			
Primary endpoint							
Moderate and severe/critical COVID-19	433	6658.36	883	6400.36	52.9%	(47.06; 58.08)	
Age 18-59 years	340	4663.76	716	4486.71	54.3%	(47.95; 59.97)	
Age >=60 years	93	1994.59	167	1913.65	46.6%	(30.74; 58.99)	
Secondary endpoints							
All SARS-CoV-2 infections	1038	6560.82	1699	6257.48	41.7%		(36.32; 46.71)
Any symptomatic COVID-19 severity	443	6656.82	895	6398.29	52.4%	(46.63; 57.64)	
Mild	10	6656.82	12	6398.29	19.9%	(-102.28; 69.00)	
Moderate	388	6658.36	707	6400.36	47.2%	(40.21; 53.51)	
Severe/ critical	46	6733.82	176	6542.13	74.6%	(64.70; 82.06)	
Asymptomatic SARS-CoV-2 infections	498	6581.00	669	6289.27	28.9%		(19.99; 36.78)
All symptomatic COVID-19 (BOD)[b] molecularly confirmed	443	6656.82	895	6398.29	54.3%	(48.55; 59.42)	
Req. Medical intervention	16	6739.75	64	6567.09	75.6%		(54.26; 88.00)
All cause mortality	19	6742.37	37	6577.25	49.9%	(10.63; 72.79)	
COVID-19 related deaths[c]	3	6742.23	17	6576.39	82.8%	(40.49; 96.77)	

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI
Supplementary Endpoints							
US FDA Harmonized COVID-19 cases	441	6657.30	884	6399.62	52.0%	(46.18; 57.32)	

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 fatality is covid-19 related if it is covid-related according to the adjudication committee or it has a fatal adverse event that is covid-19 related after the onset of a covid-19 episode with at least 1 documented PCR
NE: Not Evaluable

[TEFSUM01C.RTF] [VAC31518\VAC31518COV3001\DBR_IA_FINAL_DB\RE_IA_FINAL_DB\PROD\TEFSUM01C.SAS] 29JUL2021, 11:00

Subgroup analysis of Vaccine Efficacy Against Moderate to Severe/Critical COVID-19

In general, subgroup analyses of the final analysis data suggest consistency of efficacy results across age categories and in those with and without comorbidities. However, data are limited in the very old participants (aged 75 and older), no efficacy data was obtained in frail subjects and long term health care residents, and only participants with stable conditions were enrolled. Data are thus lacking in individuals with uncontrolled underlying disease and in those with several underlying diseases. There is no data on immunocompromised persons due to condition or immunosuppressive therapies. Efficacy was lower in HIV+ participants, but numbers are small and data difficult to interpret without taking account of other characteristics and variants.

Efficacy was much higher in the US compared to Latin America and South Africa. In the US, VE against moderate to severe/critical COVID-19 was 73% for cases with onset at least 28 days after vaccination, and similar to what was observed during the primary analysis (cut off, 22 Jan 2021). But the FU period is very short in the US, and unblinding occurred earlier. Most cases were captured early, and the reference variant was overrepresented in the US compared to other countries. The most important driving factor of VE is the type of variant.

Efficacy estimates are systematically higher against severe COVID-19 compared to symptomatic COVID-19. Despite lower number of cases, there is much less variability in the efficacy estimates for severe COVID-19 compared to symptomatic COVID-19. Subgroup analyses across age categories, for participants with/without comorbidities, and according to region show fairly similar point estimates.

Vaccine Efficacy by Virus Variant

No analysis of efficacy per variant was performed at the ime of the initial conditional MA as the 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 was planned upon completion of the sequencing. Sequencing as presented now is not yet fully complete.

At initial conditional MA, 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.

After the primary analysis cut-off, the reference sequence disappeared and several SARS-CoV-2 variants emerged over time.

At final analysis, efficacy against molecularly confirmed moderate/severe COVID-19 was higher for the reference strain compared to pooled variant strains: 71.5% (95% CI: 57.31; 81.39) and 43.6% (95% CI: 34.19; 51.67), respectively, when evaluated at least 14 days after vaccination; 58.2% (95% CI: 34.96; 73.72) and 44.1% (95% CI: 34.35; 52.56), respectively, when evaluated at least 28 days after vaccination.

For molecularly confirmed moderate/severe COVID-19 (ie. symptomatic COVID-19), variability in terms of efficacy against the variants is important. There is much less variability in terms of efficacy against the variants for severe COVID-19 than for symptomatic COVID-19, despite lower number of cases. The

point estimate of efficacy against severe COVID-19 was higher for the reference variant (around 90%) compared to all other variants pooled (around 70%).

A summary of vaccine efficacy against symptomatic and severe COVID 19 by variant strain 14 days and 28 days following a single-dose is provided in Table 13.

Table 13 Summary of vaccine efficacy against symptomatic[a] and severe[b] COVID 19 by variant strain following a single-dose

Variant	Onset	Severity	
		Symptomatic COVID-19 % Vaccine Efficacy (95% CI)	**Severe COVID-19 % Vaccine Efficacy (95% CI)**
Reference	At least 14 days after vaccination	71.5% (57.31; 81.39)	89.7% (57.33; 98.84)
	At least 28 days after vaccination	58.2% (34.96; 73.72)	93.1% (54.39; 99.84)
Alpha (B.1.1.7)	At least 14 days after vaccination	70.1% (35.13; 87.55)	51.1% (-241.18; 95.58)
	At least 28 days after vaccination	70.2% (35.27; 87.58)	51.4% (-238.95; 95.61)
Beta (B.1.351)	At least 14 days after vaccination	38.1% (4.20; 60.43)	70.2% (28.35; 89.21)
	At least 28 days after vaccination	51.9% (19.06; 72.19)	78.4% (34.46; 94.69)
Gamma (P.1)	At least 14 days after vaccination	36.4% (13.87; 53.20)	63.3% (18.28; 85.00)
	At least 28 days after vaccination	36.5% (14.05; 53.30)	63.6% (18.81; 85.10)
Zeta (P.2)	At least 14 days after vaccination	64.8% (47.32; 76.95)	91.1% (38.83; 99.79)
	At least 28 days after vaccination	64.1% (42.45; 78.30)	87.9% (9.42; 99.73)
Mu (B.1.621)	At least 14 days after vaccination	35.8% (1.49; 58.56)	79.4% (38.05; 94.91)
	At least 28 days after vaccination	35.9% (1.69; 58.65)	79.5% (38.45; 94.94)
Lambda (C.37)	At least 14 days after vaccination	10.0% (-39.53; 41.99)	67.4% (-30.62; 94.32)
	At least 28 days after vaccination	10.1% (-39.23; 42.11)	67.6% (-29.77; 94.36)
Delta (B.1.617.2/AY.1/AY.2)	At least 14 days after vaccination	-6.0% (-178.30; 59.15)	NE* NE*
	At least 28 days after vaccination	-5.7% (-177.71; 59.23)	NE* NE*
Other	At least 14 days after vaccination	73.2% (65.40; 79.40)	81.4% (59.84; 92.45)
	At least 28 days after vaccination	69.0% (59.10; 76.79)	75.7% (46.18; 90.33)

[a] Symptomatic COVID-19 requiring positive RT-PCR result and at least 1 respiratory sign or symptom or 2 other systemic signs or symptoms, as defined in the protocol.
[b] Final determination of severe COVID-19 cases was made by an independent adjudication committee, who also assigned disease severity according to the definition per FDA guidance.
* If less than 6 cases are observed for an endpoint then the VE will not be shown. NE = not estimable.

Vaccine Efficacy Against COVID-19 Requiring Medical Intervention and COVID-19 related Death

Of the 484 vs 1067 molecularly confirmed COVID-19 moderate-to-severe COVID-19 cases that occurred respectively in the Ad26.COV2.S group and placebo group at least 14 days after vaccination, only 18 vs 74 cases required medical intervention (hospitalization, ICU admission, mechanical ventilation, ECMO). In summary, respectively 5/18 cases in the vaccine group and 17/74 cases in the placebo group required ICU admission, 4/18 (Ad26) and 8/74 (placebo) required mechanical ventilation and no cases were noted with ECMO.

Vaccine Efficacy against Asymptomatic SARS-CoV-2 Infections

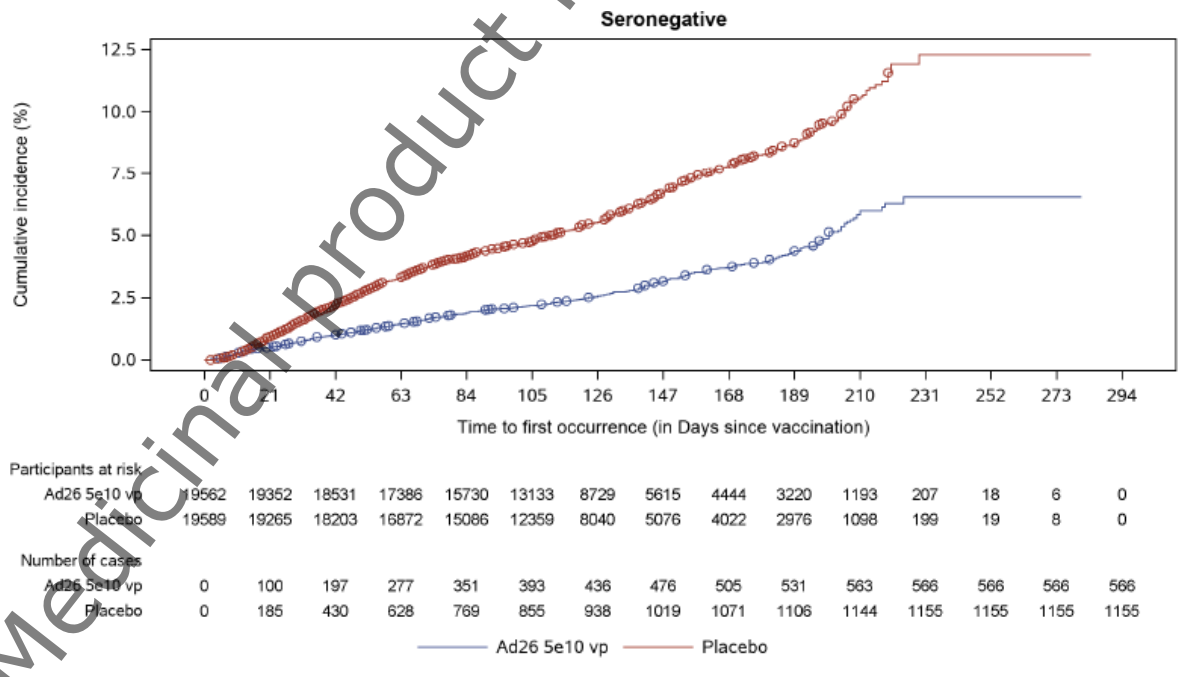
Undetected/asymptomatic COVID-19 cases were ascertained either based on serologic testing (seroconversion to the SARS-COV-2 N protein based on a Nucleoprotein assay) or a positive PCR. In practice, the majority were detected by seroconversion, as serologic testing was done in all participants at regular timepoints.

At the time of the final analysis of the double-blind phase, the estimated VE (adjusted 95% CI) against asymptomatic SARS-CoV-2 infection (at least 29 days after vaccination), was 28.9% (19.99; 36.78) as of 28 days after vaccination.

Onset and Durability of Protection

KM curves indicate that for symptomatic COVID-19, the onset of protection is 14 days after vaccination (see *Figure 18*).

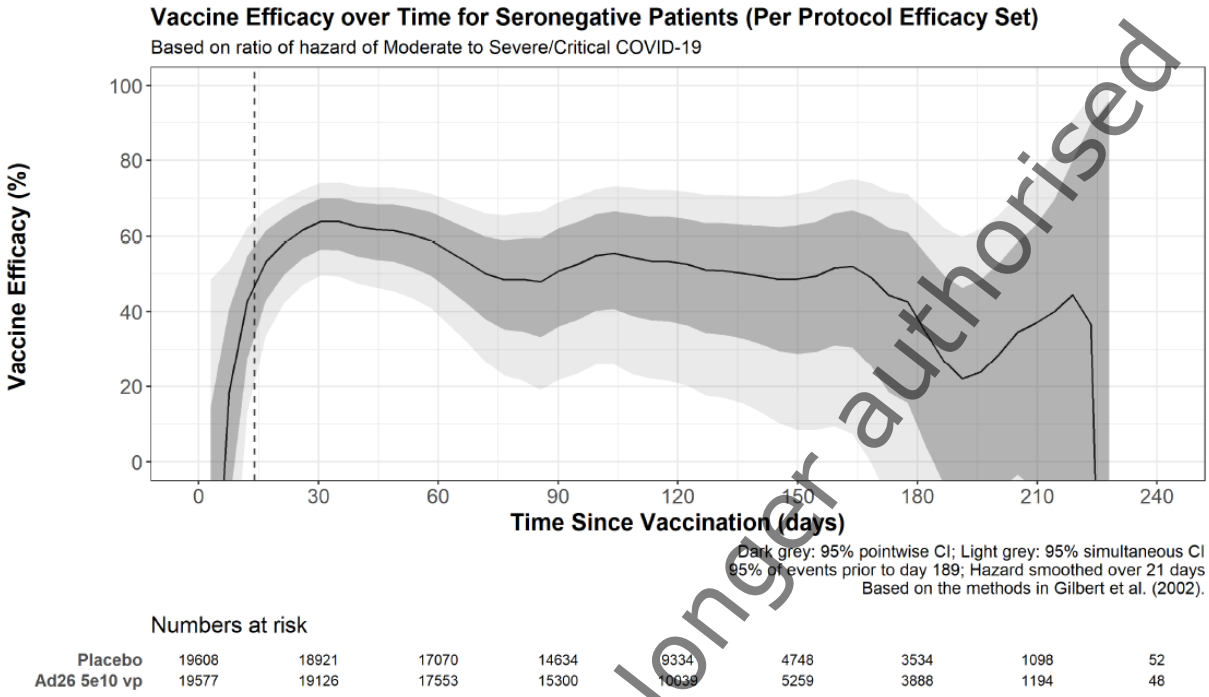
Figure 18: Cumulative Incidence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases with Onset at Least 1 Day After Vaccination by Serostatus; Per Protocol Set (Study VAC31518COV3001)



Baseline Seronegative subjects is based on the serological test at baseline (independent of the PCR result at baseline), Baseline Seropositive subjects is based on serological test at baseline(independent of the PCR result at baseline)
Severe cases are marked on the graph.
Adapted from [GEFPE03BPP.RTF] [VAC31518\VAC31518COV3001\DBR_IA_FINAL_DB\RE_IA_FINAL_DB\PROD\GEFPE03BPP.SAS] 28JUL2021, 14:12

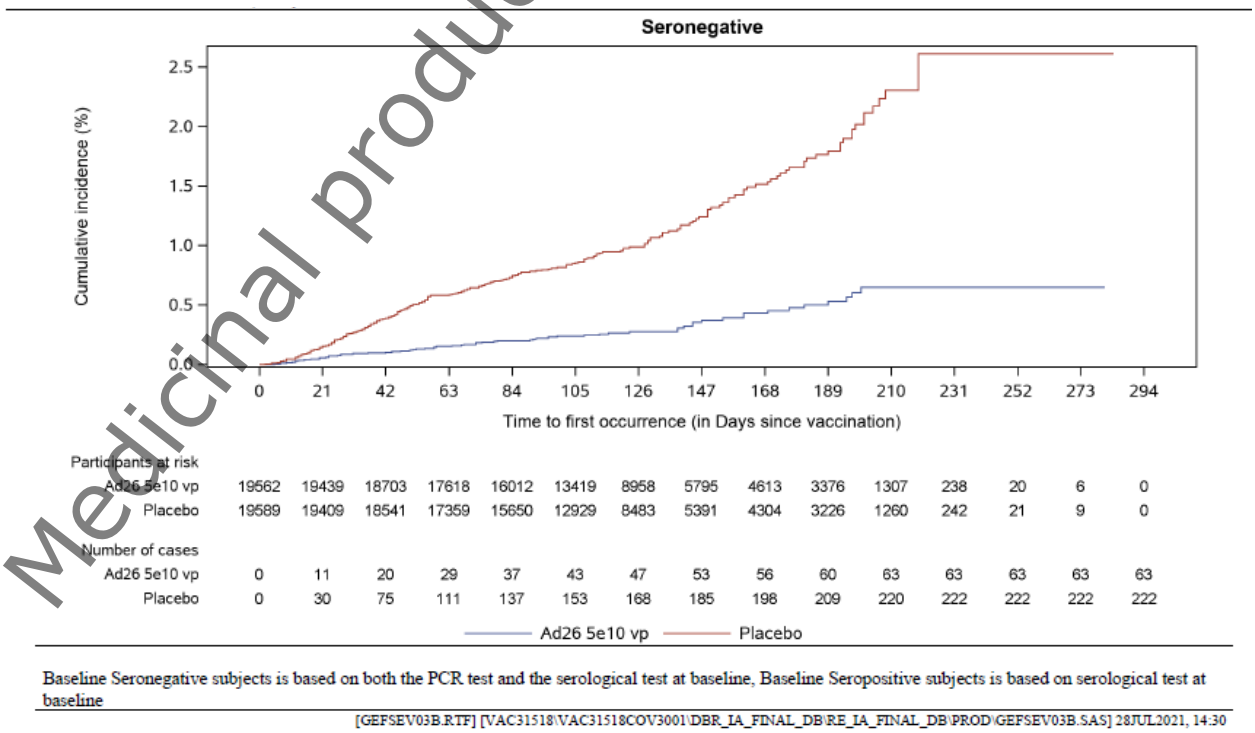
Figure 19 models efficacy against symptomatic COVID-19 over time. The uncertainty increases over time, as the number of subjects remaining in the analysis is decreasing.

Figure 19: Vaccine Efficacy Over Time of Molecularly Confirmed Moderate to Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination, PP Set (Seronegative; Study VAC31518COV3001) Final Analysis of Double-Blind Phase



For severe COVID-19, the onset of protection might be slightly earlier, around 7 days after vaccination.

Figure 20: Cumulative Incidence of Molecularly Confirmed Severe/Critical COVID-19 Cases with Onset at Least 1 Day After Vaccination By Serostatus; Per Protocol Set (Study VAC31518COV3001)

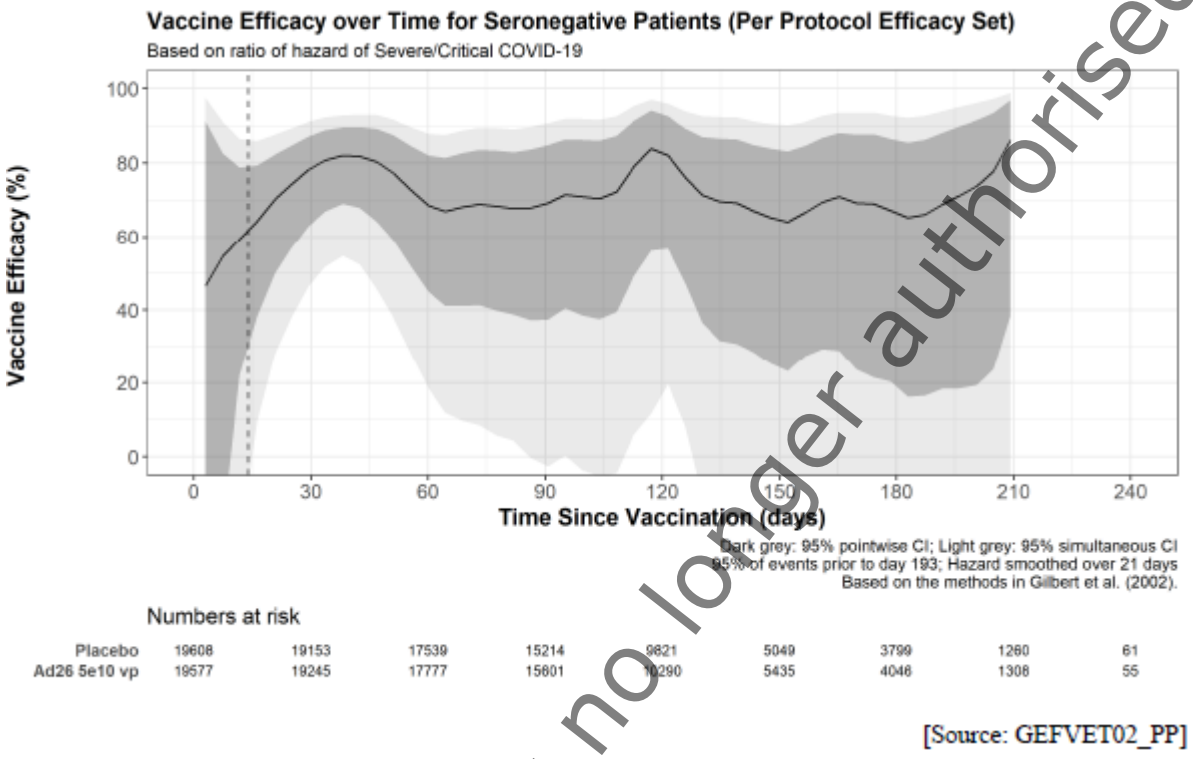


Baseline Seronegative subjects is based on both the PCR test and the serological test at baseline, Baseline Seropositive subjects is based on serological test at baseline

[GEFSEV03B.RTF] [VAC31518\VAC31518COV3001\DBR_IA_FINAL_DB\RE_IA_FINAL_DB\PROD\GEFSEV03B.SAS] 28JUL2021, 14:30

Figure 21 shows that efficacy against severe COVID-19 remains quite stable over time during 6 months, despite the appearance of new variants.

Figure 21: Vaccine Efficacy Over Time of Molecularly Confirmed Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination, PP Set (Seronegative; Study VAC31518COV3001) Final Analysis of Double-Blind Phase



[Source: GEFVET02_PP]

Efficacy by variants over time:

Onset of protection by variant:

It is not possible to conclude if onset of protection might be later for certain variants compared to the reference strain, as the cases appeared later in the study for many variants: 3 weeks after vaccination for Beta and Zeta/P2, 2 months after vaccination for Alpha, Lambda/C37 and Gamma/P1, 4 months after vaccination for Mu/B.1.621, and 5-6 months after vaccination for Delta.

Efficacy over time by variant:

To further characterize VE by variants versus waning over time, VE estimates against moderate/severe disease by time intervals and variants were provided. The MAH also provided KM curves over time for the variants.

Efficacy data for the reference strain are available only up to about 4 months post-vaccination, and for the Alpha, up to about 5 months post-vaccination. It is not known if efficacy would decrease afterwards. Efficacy point estimates are low for Gamma and Lambda, whatever the time period (from 2 to 6 months post-vaccination).

Still, number of cases and period are limited. Efficacy trends over time by variants are not robust data, and do not allow to fully disentangle the reasons for the trend of overall efficacy over time (variants and/or declining protective immunity). Nevertheless, although limited data, both cumulative incidence

curves over time for the variants and exploratory analyses of efficacy over time stratified by variants do not suggest a waning of efficacy over the study duration.

Vaccine Efficacy in Baseline SARS-CoV-2 Seropositive Participants

In the 4,214 participants (PP set) with serological evidence of past infection with SARS-CoV-2), efficacy against moderate/severe COVID-19 was 76.2% (11.97; 95.70) when evaluated 14 days after vaccination (based on 3 vs 12 cases in the Ad26.COV2.S group and placebo group, no severe cases), at final analysis.

The effect of natural infection was estimated to be around 90% in the placebo subjects (comparing incidence rates in placebo participants between baseline SARS-CoV-2 positive and negative participants).

Phase 3 Study COV3009

Criteria for analysis and subjects disposition

The MAH presents preliminary results of the primary/final analysis of the double-blind phase of the COV3009 (ENSEMBLE 2). The cut-off data for this analysis is 25 June 2021.

Analysis sets:

For COV3009, the primary efficacy analysis was performed in the Per Protocol (PP) Efficacy Set.

It was clarified that both in COV3001 and in COV3009, the analysis for efficacy excludes participants with an infection within 14 days since the last vaccination. In study COV3001 there is no blood sample at Day 14, hence exclusion of participants is based on a positive PCR result prior or at Day 14. For study COV3009, in which there is a blood sample at Day 71, exclusion is done based on PCR as well as serology) test results of Day 71.

An analysis was also done in a similar population, but who received at least the first dose of study vaccine in the double-blind phase, the Per Protocol First Dose Efficacy Set (PPFD).

Analysis Sets	**Description**
Enrolled	The enrolled analysis set includes all participants who signed the ICF and who were not screen failures.
Randomized	The randomized analysis set includes all participants who were randomized in the double-blind phase of the study.
Full Analysis Set (FAS)	All randomized participants with at least one documented study vaccine administration in the double-blind phase and met inclusion criterion 1, regardless of the occurrence of protocol deviations and serostatus at enrollment.
Per Protocol Efficacy Set (PP; primary efficacy analysis set)	Participants in the FAS who received 2 doses of study vaccine and who are seronegative at the time of 1st vaccination and at Day 71, and who have no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine before unblinding. Participants who became aware of their study vaccine allocation ceased to be part of the PP population.

Per Protocol First Dose Efficacy Set (PPFD)	Participants in the FAS who received at least the first dose of study vaccine in the double-blind phase and who were PCR negative at the time of first vaccination, who are not seropositive at baseline and who have no major protocol deviations before unblinding that were judged to possibly impact the efficacy of the vaccine specified below in the definition.

FAS:

A total of 31,300 participants were randomized and vaccinated in the double-blind phase of the study (15,708 in the Ad26.COV2.S group and 15,592 in the placebo-group), which is corresponding to the target sample size of 30,000 (15,000 in each group).

Individual unblinding and early termination:

Of the FAS, 4.5% (n=701) vs 11.3% (n=1758) respectively in the vaccine vs placebo groups **terminated the study** prematurely during the double blind phase (mainly withdrawal). Withdrawal after having been unblinded was more frequent in the placebo group (748 in the placebo group and 468 in the Ad26 group).

Treatment discontinuation concerned participants that did not receive their booster dose (second dose) 13.5% (n=2124) vs 24.0% (n=3744) **terminated the treatment** participation prematurely during the double-blind phase of the trial, respectively in the vaccine vs placebo groups. One of the reason for discontinuation of the study vaccine was administration of another COVID-19 vaccine received outside of the study (279 and 1,420 in the Ad26 group and placebo group, respectively). More participants in the placebo group were not allowed to receive the booster dose (second dose) in the double-blind phase of the study (treatment discontinuation) because they received a COVID-19 vaccine outside of the study (1,420 in the placebo group versus 279 in the vaccine group).

The proportion of participants who were unblinded prematurely before the unblinding visit was balanced (4,267 ie. 27.2% in the Ad26.COV2.S arm and 4,680 ie. 30.0% in the placebo arm).

Unblinding after Emergency Use Authorisation (EUA)

Participants could be unblinded as soon as eligible for another authorized/approved vaccine. In addition, like the COV3001, shortly following EUA in the US, participants were systematically unblinded at the unblinding visit and those who originally received placebo were offered a single dose of the vaccine. Most of the participants (98%) were actually unblinded at the cutoff date for the final analysis. Placebo subjects were offered Ad26.COV2.S during the open-label phase of the trial. Overall, 7,667 from the placebo group (49%) actually received a single dose of Ad26.COV2.S.

Participants (also those who crossed over) continue to be followed in the open-label phase of the study.

This resulted in a short follow up time up in the blind phase, and also in a large proportion of the subjects who did not receive their booster dose (second dose) yet when unblinding occurred. Participants in the active arm who had not yet received their second vaccination at the time of unblinding received the second vaccination in an open-label fashion. About half of the subjects received only one dose, and about half received their two doses during the blind phase (see below impact on PP set).

PP set:

The primary efficacy analysis was performed in the Per Protocol (PP) Set which includes participants who received both study vaccines in the double-blind phase and who were not seropositive at baseline.

Of the total of 31,300 participants vaccinated in the double-blind phase (FAS), 14,492 were part of the PP set (7484 in the Ad26.COV2.S group and 7008 in the placebo-group).

The main reasons for exclusion from the PP set were: receiving only the first vaccination in the double-blind phase and seropositivity for SARS-CoV-2 at the time of first vaccination or within 14 days after the second vaccination, which were reported for 14,549 (86.6%), 3,478 (20.7%), and 1,819 (10.8%) participants, respectively. Other reasons (all other reasons combined) were reported in 9.3% of participants. Overall, major protocol deviations were reported for 3,109 (9.9%) participants, 1,263 (8.0%) in the Ad26.COV2.S group and 1,846 (11.8%) in the placebo group. In total, 7.1% participants in the placebo group received a disallowed concomitant treatment, mainly another COVID-19 vaccine or treatment, compared to 3.2% participants in the Ad26.COV2.S group.

Approximately half of the subjects were excluded from the PP analysis set mainly because unblinding was before they had the opportunity to receive the booster dose (second dose). These participants received only one dose before unblinding. Participants who received a single dose of Ad26.COV2.S before unblinding under amendment 4 were not allowed to receive the booster dose (second dose) in the open label phase. Given the huge discrepancy between the FAS and the PP, this analysis cannot be considered as resulting from a randomized comparison, as only a limited non-random subgroup of the initial ITT population is included in the analysis.

PPFD:

Of the total of 31,300 participants vaccinated in the double-blind phase (FAS), 27,200 were part of the Per Protocol First Dose Efficacy Set (PPFD) set (13,578 in the Ad26.COV2.S group and 13,622 in the placebo-group).

Follow up duration:

In the PP set, the median follow up after the second blind vaccination was only 36.0 days (min-max: 0-172). The median was 36.0 days and 35.0 days respectively in the Ad26.COV2.S and placebo-group. 29% had at least 2 months double blind follow up post-second vaccination. As a result, the number of COVID-19 cases available for evaluation of the booster dose (second dose) is limited.

In the PPFD set, the median follow up after the first blind vaccination was 55.0 days (min-max: 0-219) and 49.5% of the participants had at least 2 months of double-blind follow-up post vaccination. The FU was shorter in the placebo group (median 58.0 days vs 49.0 days), consistently with the above data on withdrawal and individual unblinding.

The follow up period is very short especially for the elderly who were enrolled in a second step and also unblinded earlier. So in terms of total person-years up to unblinding, elderly subjects are much less represented in COV3009 compared to COV3001.

Demographics and baseline characteristics

Of the vaccinated participants (FAS), most were enrolled in Europe (41.0%, Belgium, Germany, Spain, France, UK) and in the US (38.9%). Others were enrolled in Latin America (8.5%, Brazil and Colombia), South Africa (6.6%) and the Philippines (5.0%). Europe was more represented in the PP (51.7%), while the US represented 36.5% of the PP, and other countries 11.8%.

There were 11% of the participants who were seropositive at baseline.

In the FAS, median age at enrolment was 53 years (min-max: 18-99 years), and 36% of the participants were 60 year or more. Subjects were younger in the PP. The median age at enrolment was 50 years (min-max: 18-99 years), and 25% of the participants were 60 year or more.

In the FAS, 41.4% had at least one comorbidity putting them at risk of severe COVID-19 at baseline. In the PP, 36.5% had a comorbidity putting them at risk of severe COVID-19 at baseline (28.3% had one comorbidity, 9.3% had two comorbidities and 3.7% had more than three comorbidities). The most

prevalent comorbidities were obesity (25.7%) and hypertension (12.3%). Of the FAS, 1.4% vs 1.1% of the participants were HIV infected, in the Ad26 5x1010 vs the placebo arm.

Overweight (BMI 25 - <30 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals were well represented in the trial, with 37.4% of the participants being overweight, and 26.3% being obese.

No relevant differences in baseline characteristics were observed between the Ad26.COV2.S group and the placebo-group in the FAS and the PP.

Variants circulation

A total of 469 cases occurred over the blind follow up period. Sequencing data are incomplete in this preliminary analysis and only available available for 319 out of the 469 cases (68%). It is important to note that only 66 (14 versus 52) of these cases were part of the primary/final analysis. Of these cases, also 66% had sequencing data available. Therefore, the data on the efficacy by variants should be interpreted with caution.

The reference strain (Wuhan B.1 D614G) was still circulating at the beginning of the study period, and then disappeared. Overall, it represents only 19 (6%) of the circulating strains that were sequenced. It was observed only in the US where it represented 23% of the sequenced cases. As the reference strain was only reported early during the study, it is not present in the PP set.

The most prevalent variants were the Alpha/B.1.1.7 and Mu/B.1.621, which represented respectively 26% and 23% of the cases in the PP set.

Most cases were due to the Alpha/B.1.17 (38%, n=122 in total; 26%, n=17 in the PP set), which circulated all through the follow up period in various countries. The Alpha variant was seen everywhere, but represented most cases in Europe, and a large proportion of the cases in the US.

There were also many cases due to the Mu/B.1.621 variant (14%, n=45 in total; 23%, n=14 in the PP set). The Mu/B.1.621 variant was seen essentially in Colombia where it represented most cases.

There were a limited number of cases due to the Beta/B.1.351 in various countries (7%, n=23 in total; n=3 in the PP set). The numbers were even more limited for the Gamma/P.1 (4%, n=13 in total; n=1 in the PP set) and the Zeta/P.2 (3%, n=10 in total; none in the PP set).

There were also a very limited number of cases of the Delta/B.1.617.2/AY.1/AY.2 variant (4%, n=13 in total; 3 in the PP set), at the end of the FU period (mainly in SA).

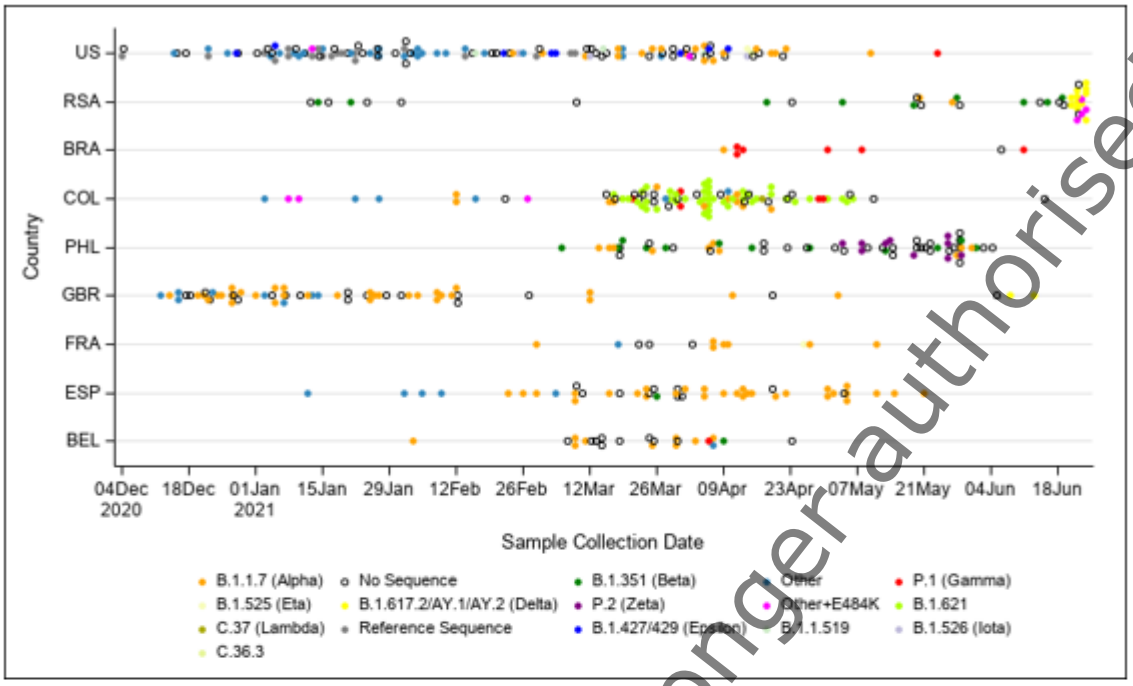
Table 14: Proportion of Molecularly Confirmed Cases Infected with SARS-CoV-2 Variant with S Protein Amino Acid Variation Versus the SARS-CoV-2 Reference Sequence with Substitution Profile for Blinded Subjects; Full Analysis Set (Study VAC31518COV3009)

	Total
Analysis Set : FAS	31300
Subset : Cases	469
Cases with sequencing data	319
Reference Sequence	19 (6.0%)
Variant Sequence	
B.1.1.7 (Alpha)	122 (38.2%)
B.1.351 (Beta)	23 (7.2%)
B.1.617.2/AY.1/AY.2 (Delta)	13 (4.1%)
B.1.427/429 (Epsilon)	8 (2.5%)
B.1.525 (Eta)	2 (0.6%)
P.1 (Gamma)	13 (4.1%)
B.1.526 (Iota)	3 (0.9%)
B.1.617.1 (Kappa)	0
C.37 (Lambda)	1 (0.3%)
P.3 (Theta)	0
P.2 (Zeta)	10 (3.1%)
B.1.621	45 (14.1%)
C.36.3	1 (0.3%)
R.1	0
B.1.1.519	3 (0.9%)
Other+E484K	9 (2.8%)
Other	47 (14.7%)

Note: The denominator is the number of cases with sequencing data available at the case episode.
Reference sequence is defined as the SARS-CoV-2 Wuhan-Hu1 Sequence with the addition of amino acid variation D614G
Amino acid variations are defined as changes from the reference sequence. Sequencing was performed using NGS Swift assay using 1% and baseline polymorphisms defined with a cut-off of 15%.
Considered Substitution Profiles:
B.1.1.7 (Alpha): H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,S982A,T716I,D1118H
B.1.351 (Beta): K417N,E484K,N501Y,D614G, A701V
P.1 (Gamma): K417T,E484K,N501Y,D614G,H655Y
B.1.617.2/AY.1/AY.2 (Delta): L452R,T478K,D614G,P681R
B.1.427/429 (Epsilon): W152C,L452R,D614G
B.1.525 (Eta): A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L
B.1.526 (Iota): L5F,T95I,D253G,D614G,E484K, A701V
B.1.617.1 (Kappa): G142D,E154K,L452R,E484Q,D614G,P681R
C.37 (Lambda): R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N
P.3 (Theta): L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F
P.2 (Zeta): E484K,D614G,V1176F (not part of P.1 or P.3)
B.1.621: T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N
C.36.3: W152R,R346S,L452R,D614G,Q677H,A899S
R.1: W152L,E484K,D614G,G769V
B.1.1.519: T478K, D614G,P681H,T732A
Other: Any sequences with mutations not leading to another variant

[TVICE_COV02_B1.RTF] [VAC31518\VAC31518COV3009\DBR_IA1\RE_IA1\PROD\TVICE_COV02_B12.SAS] 09SEP2021, 16:55

Figure 22: Occurrence Over Time of SARS-CoV-2 Variants for Blinded Subjects, Including Cases Not Sequenced; Full Analysis Set (Study VAC31518COV3009)



Cut-off date for the primary analysis: 25 June 2021.
Last unblinding visit 21-25 June 2021, except Germany 25 May 2021
Reference sequence is defined as the SARS-CoV-2 Wuhan-Hu1 Sequence with the addition of amino acid variation D614G
Sequencing was performed using NGS Swift assay using 1% and baseline polymorphisms defined with a cut-off of 15%.
Amino acid variations are defined as changes from the reference sequence.
Considered Substitution Profiles:
B.1.1.7 (Alpha): H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,S982A,T716I,D1118H
B.1.351 (Beta): K417N,E484K,N501Y,D614G, A701V
P.1 (Gamma): K417T,E484K,N501Y,D614G,H655Y
B.1.617.2/AY.1/AY.2 (Delta): L452R,T478K,D614G,P681R
B.1.427/429 (Epsilon): W152C,L452R,D614G
B.1.525 (Eta): A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L
B.1.526 (Iota): L5F,T95I,D253G,D614G,E484K, A701V
B.1.617.1 (Kappa): G142D,E154K,L452R,E484Q,D614G,P681R
C.37 (Lambda): R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N
P.3 (Theta): L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F
P.2 (Zeta): E484K,D614G,V1176F (not part of P.1 or P.3)
B.1.621 (Mu): T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N
C.36.3: W152R,R346S,L452R,D614G,Q677H,A899S
R.1: W152L,E484K,D614G,G769V
B.1.1.519: T478K, D614G,P681H,T732A
Other: Any sequences with mutations not leading to another variant
Case accrual by variants where sequence data were available.
FAS analysis set (N=31,300); cases: 468; cases with sequencing data: 319
VOC: variant of concern (only 1 variant designated as VOC (CDC.gov 2021)
[GVICE_GOV01A1.RTF] [VAC31518\VAC31518COV3009\DBR_IA1\RE_IA1\PROD\GVICE_COV01BA12.SAS] 27AUG2021, 18:55

Overall Vaccine Efficacy

The below table summarizes the main results of the analyses up to the end of double-blind phase (primary/final analysis) for the PP set.

Table 15: Summary of Vaccine Efficacy Against COVID-19 With Onset at Least 14 Days After Second Vaccination; Per Protocol Set (Study VAC31518COV3009)

	Ad26 5e10 vp		Placebo				
	#Cases	(N)/Person-Years	#Cases	(N)/Person-Years	VE	95% CI	Adjusted 95% CI
Analysis set: Per protocol set		(7484)		(7008)			
Risk set[a]		(6024)		(5615)			
Primary endpoint							
Moderate and severe/critical COVID-19	14	1729.99	52	1594.98	75.2%		(54.55; 87.30)
Age 18-59 years	10	1386.93	41	1276.36	77.6%	(54.44; 89.97)	
Age >=60 years	4	343.06	11	318.61	66.2%	(-13.97; 92.16)	
Secondary endpoints							
All SARS-CoV 2 infections molecularly and/or serologically confirmed	60	1729.35	113	1593.37	51.1%		(29.50; 66.45)
Any symptomatic COVID-19 molecularly confirmed	14	1729.99	53	1594.92	75.6%	(55.48; 87.52)	
Mild	0	1729.99	1	1594.92			
Moderate	14	1729.99	44	1594.98	70.7%	(45.46; 85.15)	
Severe/ critical	0	1730.72	8	1598.87	100.0%		(32.62; 100.00)
Asymptomatic SARS-CoV-2 infections	40	1729.88	56	1593.49	34.2%		(-6.44; 59.78)
All symptomatic COVID-19 (BOD)[b] molecularly confirmed	14	1729.99	53	1594.92	77.0%		(57.77; 87.15)
Req. Medical intervention	0	1730.72	5	1599.05			
All cause mortality	1	1730.72	1	1599.44			
COVID-19 related death [c]	0	1730.72	1	1599.44			
Supplementary Endpoints							
US FDA Harmonized COVID-19 cases	12	1730.14	52	1595.06	78.7%	(59.61; 89.66)	

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 is all subjects of the Per Protocol Set excluding subjects who had a positive PCR test between day 1 and 70 and subjects who discontinued prior to 14 days post-dose 2.
[b]BOD: Burden Of Disease is a weighted version of the mild, moderate, and severe/critical vaccine efficacies.
[c]A fatality is covid-19 related if it is covid-related according to the adjudication committee or it has a fatal adverse event that is covid-19 related after the onset of a covid-19 episode with at least 1 documented positive PCR.
NE: Not Evaluable

Adapted from [TEFSUM01A.RTF] [\VAC31518\VAC31518COV3009\DBR_IA1\RE_IA1\PROD\TEFSUM01A.SAS] 27SEP2021, 08:53

The analysis considers events that occurred at least 14 days after the booster dose (second dose) (ie. 71 days after initial vaccination).

In total, there are 66 (14 vs. 52) events of **moderate-to-severe** COVID-19 (primary endpoint), with a point estimate of 75% (75.2%; 95% CI: 54.55; 87.30), for efficacy as of Day 71 (15 days post-dose 2). An inferential analysis was done, and the lower limit of the CI was above 30%.

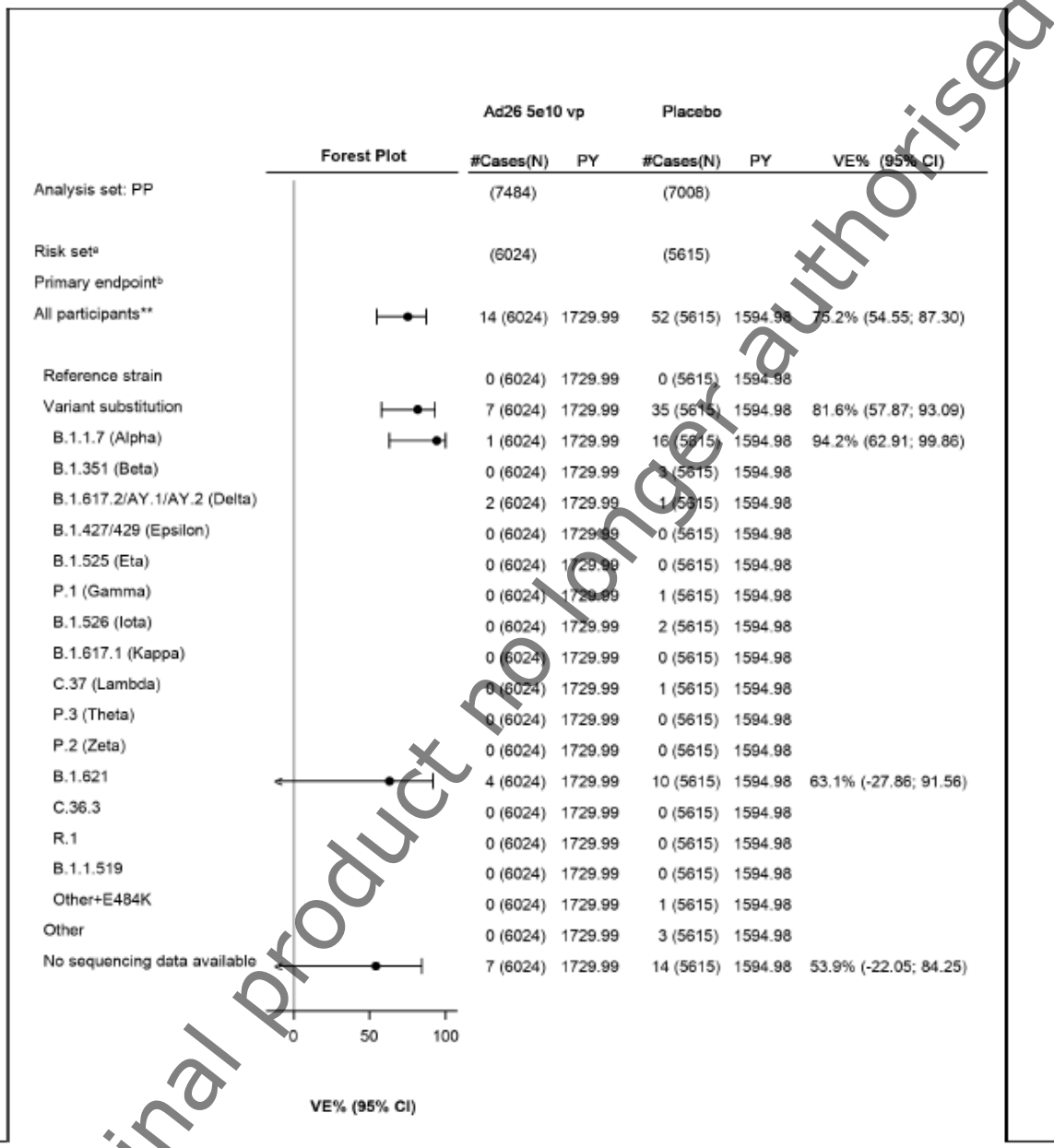
For **severe COVID-19 cases**, high efficacy (100.0%; 95% CI: 32.62; 100.00) is observed in COV3009, but the number of events is very limited (0 vs. 8), and the lower limit of the 95% CI is very low (around 30%). It is not possible to conclude whether there is an additional value for two doses compared to a single dose in terms of severe disease.

For asymptomatic infection, efficacy had a point estimate of 34% in COV3009.

Vaccine efficacy by variants:

The figure below provides a summary of the vaccine efficacy by virus variant for moderate to severe COVID-19 at least 14 days after the booster dose (second dose) in study COV3009.

Figure 23: Summary of Vaccine Efficacy of First Occurrence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 Days After Second Vaccination by Virus Variant; Per Protocol Set (Study VAC31518COV3009)



PY: Person Years; VE: Vaccine Efficacy; CI: Confidence Interval; PP: Per Protocol Set; NE: Not Evaluable.
[a]The risk set is all subjects of the Per Protocol Set excluding subjects who had a positive PCR test between day 1 and day 70 and subjects who discontinued prior to 14 days post-dose 2.
[b]Moderate to Severe/Critical Covid-19 cases.
The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions (** indicates adjusted CI).
If less than 6 cases are observed for an endpoint then the VE will not be shown.
Seronegativity and seropositivity are based on the serological tests at baseline and at Day 71.

Estimates could be provided only for the Alpha and the Mu variants in COV3009.

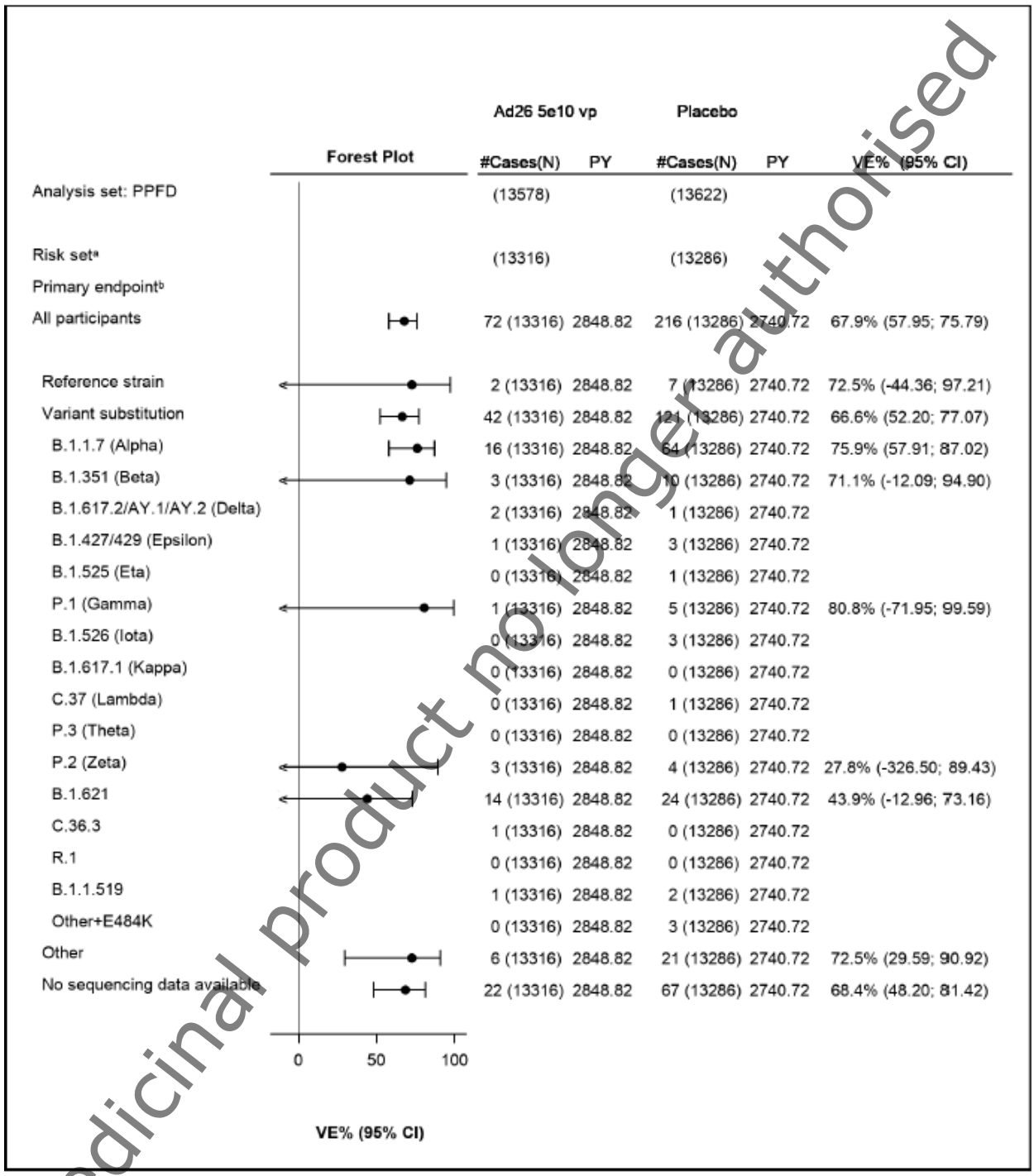
For events with onset at least 14 days after the second vaccination, efficacy for the Alpha/B.1.1.7 was (94.2% [95% CI: 62.91; 99.86]). Therefore, the estimate is higher compared to the estimate in COV3001, but with widely overlapping CIs.

Efficacy was not demonstrated for the Mu/B.1.621 variant in the COV3009 as the lower bound of the 95%CI is below 0 (63.1 [95% CI: -27.86; 91.56]). Therefore, although the efficacy point estimate was higher for the two dose schedule trial compared to the single dose schedule trial for this variant, no conclusion can be draw given the lack of precision of the estimate.

There were only very few cases for the other variants. In particular, there were insufficient Delta cases for meaningful analysis (2 vs 1 for the Delta).

Of the 66 cases in the PP, sequencing data were available for 45 cases 7/14 in the active group and 38/52 in the placebo group. Hence there is an imbalance between the arms in terms of the proportions on non-available sequencing data (50% vs. 27% in the vaccine vs. the placebo group).

Figure 24: Summary of Vaccine Efficacy of First Occurrence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 Days After First Vaccination by Virus Variant; Per Protocol First Dose Efficacy Set (Study VAC31518COV3009)



PY: Person Years; VE: Vaccine Efficacy; CI: Confidence Interval; PPFD: Per Protocol First Dose Efficacy Set; NE: Not Evaluable.

[a]The risk set is all subjects in the Per Protocol Set excluding subjects who had a positive PCR test between day 1 and day 14 and subjects who discontinued prior to day 15.

[b]Moderate to Severe/Critical Covid-19 cases.

If less than 6 cases are observed for an endpoint then the VE will not be shown.

Seronegativity and seropositivity are based on the serological tests at baseline.

Adapted from [GEPPE10E.RTF] | [VAC31518\VAC31518COV3009\DBR_IA1\RE_IA1\PROD\GEPPE10E.SAS] 27SEP2021, 09:10

Vaccine efficacy after the first vaccination:

After the first vaccination (events with onset at least 14 Days After First Vaccination; Per Protocol First Dose Efficacy Set), efficacy point estimates were 67.9% (95% CI: 57.95; 75.79) overall, which is a similar point estimate as in COV3001. Efficacy was 75.9% (57.91;87.02) for the Alpha variant, and 43.9% (-12.96;73.16) for the Mu variant, which is also consistent with what was observed in COV3001.

Overall results PD1 are consistent with COV3001. It is assumed that those results are mainly reflecting efficacy of a single dose (and not the efficacy of the two doses), as the person-years PD1 to PD2 are overall more represented in the analysis compared to the person-years PD2.

Vaccine Efficacy Against All Symptomatic COVID-19 and Any SARS-CoV-2 Infection

Noticeably, efficacy against asymptomatic SARS-CoV-2 infection with onset at least 14 days after the second vaccination was poor 34.2% (-6.44; 59.78), which is similar as in the COV3001.

Subgroup Analysis

The subgroup analyses do not raise concern of lack of efficacy for particular subgroups (including age group, conmorbidities, gender…) but the number of cases (length of follow up) was very limited in some of the subgroups. Estimates were very imprecise in the elderly (60 years or more).

There are large regional differences in terms of efficacy were observed. In the US, VE (95% CI) against moderate to severe/critical COVID-19 at least 14 days after the booster dose (second dose) was 93.7% (58.45; 99.85). In the US, the predominant variant during the study was the Alpha. Observed VE in other regions was lower (60.0%-68.8%), which was possibly driven by reduced VE against certain SARS-CoV-2 variants.

4.3. Discussion

The MAH started the efficacy trial COV3001 assessing a single-dose schedule at the end of September 2021. In November 2021, the MAH also started the efficacy trial COV3009, assessing a two-dose schedule 2 months apart. The aim was to propose a single dose regimen for emergency pandemic situations, and a two-dose regimen for routine use after the pandemic. Based on their experience with the Ad26 platform with other antigens, the MAH assumed that a second vaccination may result in a more durable immune response. Because of the emergency situation, the MAH decided to conduct two trials separately in order to show efficacy as fast as possible for the single dose schedule.

Available and expected data:

Efficacy results are presented up to the end of the double-blind phase for the **COV3001** study (single dose schedule) with a median FU of approximately 4 months (final analysis, cut-off date 9 July 2021). At intial conditional MA, data were submitted with a median FU of approximately 2 months (primary analysis, cut-off date of January 22). The primary analyses results are discussed in the initial conditional MA report.

The MAH also presents preliminary efficacy results of the primary/final analysis of the double-blind phase of the **COV3009** (2-dose schedule) (cut-off date 25 June 2021).

Additional analysis for all clinical trials are planned to be generated and should be made available (refer to ANNEX: New recommendations introduced in this procedure).

Design of study **COV3001**:

The design of **COV3001** was assessed as part of the initial conditional MA.

COV3001 is a randomized, double-blind, placebo-controlled, Phase 3 study performed in adults ≥18 years of age. The study was conducted in the US, several Latin American countries (Argentina, Brazil, Chile, Peru, Mexico, Colombia), and South Africa. Participants were randomized in parallel in a 1:1 ratio to receive Ad26.COV2.S at a dose level of $5x10^{10}$ vp or placebo intramuscularly. Participants with stable medical conditions were allowed to participate in the study, but immunocompromised persons due to condition or immunosuppressive therapies were excluded.

The primary objective of study COV3001 is to evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe 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 co-primary endpoints consist in a combination of moderate COVID-19 and severe COVID-19. 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' used for other vaccines.

Moderate COVID-19 is a composite endpoint which in practice also includes cases that would be considered mild by other definitions. The definition for severe 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 were adjudicated in a blinded manner by the Clinical Severity Adjudication Committee (CSAC).

The secondary objectives include the evaluation of efficacy in the prevention of molecularly confirmed severe COVID-19 and COVID-19 requiring medical intervention, and confirmed asymptomatic/undetected infections with SARS-CoV-2 (using SARS-CoV-2 N protein seroconversion).

Design of study **COV3009**:

COV3009 is a randomized, double-blind, placebo-controlled Phase 3 study. The design and endpoints are similar to the COV3001 trial. The study was conducted in Europe and the US mainly, which differs from COV3001 that included no European site. Participants were randomized in a 1:1 ratio to receive 2 doses of Ad26.COV2.S at a dose level of 5x1010 vp 56 days apart or placebo intramuscularly.

The sample size calculation for this trial was driven by the primary analysis which aimed to demonstrate VE>30% with the per protocol population. The target sample size for the study was approximately 30,000 participants (≈15.000 patients per group) and 104 overall events for the per protocol population. No interim analysis was planned to prematurely stop the trial for overwhelming efficacy. A graphical approach was planned to handle multiplicity along the primary endpoint and the secondary confirmatory endpoints. The operating characteristics, the statistical assumptions and the planned sample size were reasonable and were expected to provide sufficient evidence basis for an adequate benefit/risk regulatory assessment.

EUA and impact on **COV3001** and **COV3009**:

After EUA in the US (February 27, 2021), both studies introduced the possibility to cross-over to the Ad26.COV2.S vaccine. So, all participants were unblinded at a scheduled study visit and participants who initially received a Placebo were offered vaccination with a single dose of Ad26.COV2.S. The cross-over resulted in an important loss of placebo-controlled follow up. All participants were encouraged to continue to be followed for up to 2 years post-vaccination as part of the open label phase.

Expected efficacy data, open label phase **COV3001** and **COV3009:**

COV3009 was designed to assess a 2-dose schedule vs placebo. It was not designed to assess superiority of a the 2-dose schedule vs a single dose schedule, or to make any direct comparison between a 2-dose and a single dose schedule. Still, in Amendment 4 (following EUA), it was planned that participants newly

enrolled in the open-label phase would be randomized in a 1:1 ratio to receive either 1 dose or 2 doses of Ad26.COV2.S. However, the sample size was reached during the blind phase. So few (n=334) participants were randomized between 2-dose vs 1-dose vaccine Due to small numbers, the comparison of those randomized groups will not provide useful data. A large sample size would have allowed useful data for a direct comparison of a single vs a 2 dose-schedule from participants recruited in parallel, within a similar epidemiological context. Instead, participants vaccinated initially with a 2-dose schedule in the blind phase will be compared, in terms of incidence rates, to participants cross-vaccinated later with a single dose schedule in the open label phase. The detailed assessment of the design and limitations of the open label phase is not in the scope of this assessment report. Nevertheless, it is considered unclear if any robust evidence on the added value of the second/booster dose will be drawn based on these analyses, at least from the efficacy perspective, given the loss of a parallel control group, the loss of blind follow up, and given that a large proportion of the participants received a vaccine from other brands. Nevertheless, data from the open label Phase, including for the Delta period, may give some insight in effectiveness of a single dose and the added value of a booster dose (second dose) for this variant, and other variants in the future.

At the moment, the interpretation of the added value of a booster dose (second dose) in terms of efficacy relies on a comparison across trials, which is associated with a lot of limitations, especially in the context of emergence of several variants.

- **COV3001**

Study population, COV3001:

In total, 43,788 participants were vaccinated (21,898 and 21,890 in the Ad26.COV2.S and placebo group) and constitute the Full Analysis Set (FAS) in COV3001.

A slightly higher proportion of subjects terminated the double blind phase prematurely in the placebo group (5.4% vs 8.8% the Ad26 and placebo group). This was mainly due to receival of another vaccine outside of the study before unblinding (3.1% and 5.6%, received another COVID-19 vaccine before unblinding. Moreover, 26% (n=5,712) of the participants from the active group and 27% (n=5,992) of the participants from the placebo group requested to be unblinded on an individual basis (but continued into the open label phase) and 670 and 1222 were vaccinated outside study (but continued the study) respectively in active and placebo groups. This raises some concern about treatment allocation awareness in the trial.

The primary and final analyses of efficacy was based on the Per-protocol Efficacy (PP) population. Of the participants in the FAS, 39,185 (19,577 and 19,608 in the Ad26.COV2.S and placebo group) were included in the PP set. Baseline seropositivity for SARS-CoV-2 was the main reason for elimination from the PP set. Other reasons were being PCR positive at baseline or protocol deviations.

The median follow up after double blind vaccination was 4 months (123 days in the FAS and 121 days [min-max]: 1-284 days in the PP). The median follow up was 122 days and 120 days in the active vs the placebo group. Overall, 22.8% of the participants had a follow up of at least 6 months (PP).

The study was conducted in the United States (44% of the FAS), various countries of Latin America (41% of the FAS), and South Africa (15% of the FAS). The proportion of participants ≥60 years was 35% (in the PP). There were only few long term care residents (0.3% in the FAS). Participants with comorbidities were well represented. At least one comorbidity was present in 40% (PP), the most common being obesity (BMI ≥30 kg/m2, 28%), hypertension (10%) and type 2 diabetes mellitus (7.5%). Only participants with stable conditions were enrolled and immunocompromised persons were excluded. Baseline characteristics were well balanced across arms, overall and within regions.

Variant circulation, COV3001:

During the double blind observation period, new SARS-CoV-2 variants emerged, with important variations across countries and over time. There was a diversity of variants, with no dominating variant over the study period. Overall, cases included the reference sequence (14%), the Gamma/P1 (13%), and the Zeta/P2 (11%), Beta/B.1.351 (8%), Mu/B.1.621 (7%), Lambda/C.37 (6%), and other variants. There were very limited cases of Alpha/B.1.1.7 (3%) and Delta/B.1.617.2 (2%). In the PP, the circulating variants over the period were the same.

The variants evolved a lot over time. At the beginning of the period, the referent variant was predominant (mainly in the US), as well as the Beta/B.1.351 (in SA), and the Zeta/P.2 (in Brazil). The reference sequence disappeared after 2-3 months, and several other variants were observed, such as the Gamma/P1 (in Brazil), and the Lambda/C37 (in Peru). At the end of the FU period cases of Mu/B.1.621 (in Colombia) and Delta/B.1.617.2 variants (in SA) were observed.

Since the variants are extremely related to the period, it is not possible to fully disentangle the effect of the variants from the effect of waning of protective immunity per se.

Key efficacy results, COV3001:

Efficacy estimates are systematically higher against severe COVID-19 compared to all symptomatic COVID-19. The point estimates of efficacy against symptomatic disease were lower at the final vs. the primary analysis, while point estimates of efficacy against severe disease were similar at the primary and the final analysis.

Symptomatic COVID-19:

In total, 484 vs 1067 cases of moderate/severe COVID-19 (primary endpoint) occurred in the active vs the placebo groups >14 days after vaccination. At the final analysis, efficacy was 56.3% (95% CI: 51.30; 60.84) and 52.9% (95% CI: 47.06; 58.08) respectively >14 days and >28 days after vaccination. At the primary analysis, the corresponding estimates were 66.9% (95% CI: 59.03; 73.40) and 66.1% (95% CI: 55.01; 74.80). There were only 26 and 22 additional mild cases (>14 and >28 days), as the primary endpoint captured most mild cases, hence corresponds to symptomatic COVID-19 of any severity.

Point estimates were thus lower at the final (4 months median FU) vs. the primary analysis (2 months median FU), but 95% CI overlap. The disappearance of the reference strain and emergence of variants later in the study probably explains the reduction in efficacy estimates between the primary analysis and the final analysis, but waning of protective immunity over time might also contribute (see below).

Severe COVID-19:

The number of severe cases was large, making the estimates robust even for severe COVID-19 cases. At the final analysis, the point estimate of efficacy against severe disease was 73.3% (95% CI: 63.94; 80.49) and 74.6% (95% CI: 64.70; 82.06) for events >14 days and >28 days after vaccination. Those estimates are in the same range as those from the primary analysis. At the primary analysis, the efficacy against severe disease was 76.7% (95% CI: 54.56; 89.09) and 85.4% (95% CI: 54.15; 96.90) for events >14 days and >28 days after vaccination respectively.

COVID-19 Requiring Medical Intervention and COVID-19 related Death:

Of the 484 vs 1067 moderate/severe COVID-19 cases that occurred respectively in the Ad26.COV2.S group and placebo group at least 14 days after vaccination, only 18 vs 74 cases required medical intervention. Respectively 5/18 cases in the vaccine group and 17/74 cases in the placebo group required ICU admission, 4/18 (Ad26) and 8/74 (placebo) required mechanical ventilation and no cases were noted with ECMO. Efficacy estimates for COVID-19 requiring medical intervention (>14 days after vaccination),

which in practice corresponds to COVID-19 related hospitalization, was 76.1% (95% CI: 56.86; 87.67). For COVID-19 related death efficacy was 84.5% (95% CI: 47.30; 97.06). Those point estimates were in line with those for severe disease. For COVID-19 related deaths, this was based on 3 vs. 19 events in respective groups.

Vaccine Efficacy by Variant in COV3001:

At the time of the initial conditional MA, no analysis of efficacy per variant was performed as 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. Sequencing data are now available for approximately 90% of the cases.

At final analysis, efficacy against **moderate/severe COVID-19** was higher for the reference strain compared to pooled variant strains: 71.5% (95% CI: 57.31; 81.39) and 43.6% (95% CI: 34.19; 51.67), when evaluated at least 14 days after vaccination. For moderate/severe COVID-19, variability in terms of efficacy against the variants is important. Considering the events with onset at least 14 days after vaccination, the efficacy point estimates are good (approx. 70%) for the reference and the Alpha variant, as well as for the Zeta/P2 variant (approx. 65%). However, the efficacy point estimate was much lower for the Beta (approx. 40%), the Gamma/P.1 (approx. 35%) and the Mu (approx. 35%) variants. For the Lambda/C.37, efficacy point estimate was approx. 10%. The limited data for the Delta variant, also point to a signal of lack of efficacy (point estimate -6%). There were 11 Delta cases in the Ad26.COV2.S group versus 10 in the placebo group, which appeared late after vaccination (5.5 months up to 7.5 months, in SA). The limited data suggest a lack of efficacy for this variant, which would be in line with some studies reporting Real world data on symptomatic disease during the Delta period. CIs are wide for certain estimates.

Efficacy against **severe COVID-19** could be estimated for some variants, and data suggest that efficacy is maintained for those variants with point estimates above 60%. For note, RWD during the Delta period seem to be in line with these observations. There is much less variability in terms of efficacy against the variants for severe COVID-19 than for symptomatic COVID-19, despite lower numbers. Nevertheless, the point estimate of efficacy against severe COVID-19 was higher for the reference strain (around 90%) compared to all other variants pooled (around 70%), 95% CIs widely overlapped. Estimates for cases occurring at least 14 days after vaccination were 89.7% (95% CI: 57.33; 98.84) for the reference variant compared to 70.0% (95% CI:54.72; 80.61) for pooled variants. It is not possible to determine efficacy against severe COVID-19 for the Alpha (2 vs. 4, in the Ad26.COV2.S group versus the placebo group all >Day 28) and the Delta (2 vs. 2, all >Day 28) variants because cases are too few.

The CSR for the final analysis of the double blind phase will be finalised this year, and will include more complete genomic analyses (approx. 90% available now) from available cases in the double blind phase, up to the cut-off date of 9 July 2021. Data of the open label FU phase up to cut-off date of 9 July will also be presented in the CSR, including genomic analyses.

Analyses for the Delta period will be provided from the open label follow up, including subjects vaccinated initially in the blind phase and later in the open label phase (vaccination of the placebo participants after unblinding).

Onset and Durability of Protection, COV3001:

Figures modelling efficacy over time and tables describing efficacy by 14 days intervals were provided.

Symptomatic COVID-19:

KM curves indicate that for symptomatic COVID-19, The onset of protection is 14 days after vaccination.

Efficacy against symptomatic COVID-19 drops rapidly after just a few weeks (around 1-2 months after vaccination). This trend could be due to a waning of protective immunity. However, after approx. 2 months, the reference strain was disappearing from the trial, and several variants accumulated, in parallel with the observed drop.

To further characterize efficacy by variant vs waning of protection over time, exploratory analyses of efficacy against moderate/severe COVID-19 by time intervals and variants were provided, as well as KM curves over time since vaccination for the variants. The periods for which data are available are limited. Efficacy data for the reference strain are available only up to about 4 months post-vaccination, and for the Alpha, up to about 5 months post-vaccination. Nevertheless, although exploratory, these analyses do not suggest a decline of efficacy over the study duration. Efficacy point estimates are very low for Gamma and Lambda, whatever the time period. Hence, these data are suggesting that the overall decline is more likely due to the variants.

In principle, it appears difficult to disentangle whether the loss of efficacy is due to waning of protective immunity or to the emergence of VOCs. However, based on the available data, including stratified analyses by variants, the trend is considered more likely related to the emergence of new variants with low efficacy. This hypothesis is also more consistent with immunogenicity data showing no obvious waning of immune responses over time over 6 months (making the hypothesis of waning less likely).

Severe COVID-19:

For severe COVID-19, the onset of protection might be slightly earlier, around 7 days after vaccination. Efficacy against severe COVID-19 remains quite stable over time during 6 months, despite the emergence of new variants. Noticeably, RW data indicate that efficacy against hospitalized COVID-19 remains quite stable over time (also against ICU admissions and deaths), including when the Delta variant appeared, while for SARS-COV-2 infection or any symptomatic COVID-19, RWD are currently inconclusive (see RWD section).

Vaccine Efficacy in Baseline SARS-CoV-2 Seropositive Participants in COV3001:

In the final analysis, efficacy against moderate/severe COVID-19 was 76.2% (95% CI: 11.97; 95.70) in participants with serological evidence of past infection with SARS-CoV-2. This is based on only 3 vs 12 cases in the Ad26.COV2.S group and placebo group at least 14 days after vaccination, and the 95% CI lower limits was 12%, well below critical 20% or 30% VE thresholds. Therefore efficacy is not demonstrated in the individuals previously infected, although point estimate is consistent with that in participants seronegative at baseline.

The final TLR/CSR up to the end of the open label phase, when last participant completes 18 months FU, will be available in the second half of 2022.

It is unclear at the moment if the open label phase will bring relevant and useful results, at least from the efficacy perspective, given the loss of a parallel control group and the loss of blind follow up. In addition, it is assumed that a large proportion of the participants received vaccine from other brands. The design and limitations of the open label phase were not assessed in this report.

- **COV3009**

Study population, COV3009:

A total of 31,300 participants were randomized and vaccinated in the double-blind phase of the study COV3009 (15,708 in the Ad26.COV2.S group and 15,592 in the placebo-group).

Of the FAS, 4.5% (n=701) vs 11.3% (n=1758) terminated the study prematurely during the double-blind phase (mainly withdrawal, which could occur after unblinding) respectively in the vaccine vs placebo

groups. Withdrawal after having been unblinded was more frequent in the placebo group (748 in the placebo group and 468 in the Ad26 group). Moreover, 13.5% (n=2124) vs 24.0% (n=3744) terminated the treatment participation prematurely (did not receive their booster dose (second dose)) during the double-blind phase of the trial, respectively in the vaccine vs placebo group. One of the reason was administration of another COVID-19 vaccine received outside of the study (279 and 1,420 in the Ad26 group and placebo group, respectively). More participants in the placebo group were not allowed to receive the booster dose (second dose) in the double-blind phase of the study because they received a COVID-19 vaccine outside of the study (1,420 in the placebo group versus 279 in the Ad26 group).

The proportions of participants who were unblinded prematurely (before the unblinding visit) were balanced (4,267 ie. 27.2% in the Ad26.COV2.S arm and 4,680 ie. 30.0% in the placebo arm). 179 and 410 participants (in the Ad26.COV2.S and placebo group) were vaccinated outside the study with a COVID-19 vaccine before being unblinded. KM presented by the MAH suggest that the follow-up time of the double-blind phase in both the PP and FAS is similar across groups. Whether awareness of treatment allocation impacted the results remains unclear.

In addition, like the COV3001, shortly following EUA in the US, participants were systematically unblinded and those who originally received placebo were offered a single dose of Ad26.COV2.S. Most of the participants (98%) were actually unblinded at the cutoff date for the final analysis and 7,667 from the placebo group (49%) received a single dose of Ad26.COV2.S during the open-label phase.

The primary efficacy analysis was performed in the PP Set which includes participants who received both study vaccines in the double-blind phase, who are seronegative at the time of 1st vaccination and at Day 71 (for N-protein ab assay), and who had no major protocol deviations that were judged to possibly impact the efficacy of the vaccine.

Of the total of 31,300 participants vaccinated in the double-blind phase (FAS), 14,492 were part of the PP set (7484 in the Ad26.COV2.S group and 7008 in the placebo-group). Actually, unblinding/cross-vaccination resulted in the exclusion of approximately half of the participants from the PP analysis set because unblinding occurred before they had the opportunity to receive the booster dose (second dose). This explains why the PP set is so limited compared to the FAS. Actually, only 54% (8,655 who received Ad26.COV2.S and 8,096 who received placebo) of the participants received 2 doses during the double-blind phase. Other reasons for exclusion from the PP set are baseline SARS-CoV-2 seropositivity (11% of the participants) and major protocol deviations. Given the huge discrepancy between the FAS and the PP, this analysis cannot be considered as resulting from a randomized comparison, as only a limited non-random subgroup of the initial ITT population is included in the analysis.

Unblinding/cross-vaccination resulted in a short follow up time in the blind phase. In the PP set, the median follow-up after the second blind vaccination was only 36 days (min-max: 0-172, 36 days and 35 days respectively in the Ad26.COV2.S and placebo-group). 29% had at least 2 months double blind follow up post second vaccination. As a result, the number of COVID-19 cases available for evaluation of the booster dose (second dose) is limited (see below).

Of the vaccinated participants (FAS), most were enrolled in Europe (41%, Belgium, Germany, Spain, France, UK) and in the US (39%). Others were enrolled in Latin America (8.5%, Brazil and Colombia), South Africa (6.5%) and the Philippines (5%). Europe was more represented in the PP (52%), while the US represented 36% of the PP, and other countries 12%. COV3001 also was conducted in the US (44%), Latin America (41%) and South Africa (15%). However, the proportion of participants from Latin America is much higher in COV3001. There was no European site in the COV3001. In the FAS, median age at enrolment was 53 years (min-max: 18-99 years), and 36% of the participants were ≥60 years. Participants were younger in the PP: the median age at enrolment was 50 years (min-max: 18-99 years),

and 25% of the participants were ≥60 years. Participants were thus younger in COV3009 compared to COV3001 (where 35% of participants ≥60 years in PP).

In addition, the follow up period is very short especially for the elderly who were enrolled in a second step and also unblinded earlier. In terms of total person-years up to unblinding, elderly participants are much less represented in COV3009 compared to COV3001. In the PP, 36.5% of participants had at least one comorbidity putting them at risk of severe COVID-19 at baseline. The most prevalent comorbidities were obesity (25.7%) and hypertension (12.3%). Only participants with stable conditions were enrolled and immunocompromised persons were excluded. No relevant differences in baseline characteristics were observed between the Ad26.COV2.S group and the placebo-group in the FAS and the PP.

Variants circulation COV3009:

Sequencing data were available from only 68% out of the 469 cases reported, and 66% of the 66 cases that occurred in the PP. There were important differences over time and across countries in terms of the circulating variants, as for the COV3001, but the distribution of variants is very different than that observed in the COV3001.

The reference strain, represents only 19 (6%) of the sequenced case. It was still circulating at the beginning of the study period, and then disappeared. It is not present in the PP set. The most prevalent variants were the Alpha/B.1.1.7 and Mu/B.1.621, which represented respectively 26% and 23% of the cases in the PP set. Alpha/B.1.17 circulated all through the follow up period in various countries. It represented most cases in Europe, and a large proportion of the cases in the US. The Mu/B.1.621 variant was seen essentially in Colombia where it represented most cases. There were very limited number of cases due to other variants such as the Beta/B.1.351, Gamma/P.1, and the Zeta/P.2. There were also a very limited number of cases of the Delta/B.1.617.2/AY.1/AY.2 variant (4%, n=13 in total; 3 in the PP set), at the end of the FU period (mainly in South Africa).

Key efficacy results, COV3009:

The number of events for the assessment of the two dose schedule is very limited (only 66 events instead of the planned 104), particularly in participants ≥60 yoa (n=15). This implies that no robust estimate can be provided within subgroups, by variants, and for severe disease. The short time of FU (36 days) also considerably limits the interpretation of the results of this study.

Efficacy against **moderate/severe** COVID-19 was 75.2% (95% CI: 54.55; 87.30) for events as of Day 71 (onset >14 days post-dose 2), this was based on 14 vs. 52 cases in the active vs. placebo groups. The effect (75%) is thus numerically larger for the primary endpoint compared to what is observed in the COV3001, which was 67% and 56% for events with an onset at least 14 days after vaccination, respectively over a median follow-up time of approximately 2 and 4 months. The difference between both trials in efficacy point estimates is however not major, and the CI overlap widely.

The point estimates are not better in the elderly in the COV3009 compared to the trial with the single dose, but conclusion cannot be drawn as numbers are very small (4 vs. 11 events).

For **severe** COVID-19 cases, high efficacy (100.0%; 95% CI: 32.62; 100.00) is observed in COV3009, but the number of events is very limited (0 vs. 8), and the lower limit of the 95% CI is very low. In COV3001, the point estimates of VE against severe COVID-19 were 76.7% over a median FU of 2 months (95% CI: 54.56; 89.09) and 73.3% (63.94; 80.49) over a median FU of 4 months (for events with an onset beyond Day 14). It is not possible to conclude whether there is a gain for two doses compared to a single dose in terms of severe disease.

A graphical approach (Bretz et al, 2009) was planned to handle multiplicity along the primary endpoint and the secondary confirmatory endpoints. According to the plan and the trial results, the primary

endpoint and "burden of disease" were analysed using a 95% two-sided confidence level, whereas for the rest of secondary confirmatory endpoints two-sided 97.5% confidence levels were used.

Vaccine efficacy by variants in COV3009:

Estimates could be provided only for the Alpha and the Mu variants.

For events with onset at least 14 days after the second vaccination, efficacy for the Alpha/B.1.1.7 was 94.2% (95% CI: 62.91; 99.86). Therefore, the estimate is higher compared to the estimate in COV3001, but with widely overlapping CIs.

Efficacy was not demonstrated for the Mu/B.1.621 variant in the COV3009 as the lower bound of the 95% CI is below 0 (63.1 [95% CI: -27.86; 91.56]). Therefore, although the efficacy point estimate was higher for the two dose schedule trial compared to the single dose schedule trial for this variant, no conclusion can be draw given the lack of precision of the estimate.

There were only very few cases for the other variants. In particular, there were insufficient Delta cases for meaningful analysis (2 vs 1 for the Delta >Day 150). There were 13 cased of Delta in total, but all other cases were asymptomatic (5 vs. 5 in the active vs placebo group all occurred >Day 140). So overall, there were 7 vs 6 Delta cases (symptomatic or not) >day 71 in the double blind phase of the trial, respectively in the active vs placebo group.

Samples were selected for sequencing if the SARS-CoV-2 viral load result was available and was above 1,000 copies/mL. No other criteria such as country or disease severity were used. Still, the sequenced subpopulation cannot be considered as a random subsample. Moreover, of the 66 cases in the PP, sequencing data were available for only 45 cases, with an imbalance between the arms in terms of the proportions on non-available sequencing date (7/14 in the active group and 38/52 in the placebo group). Overall, estimates by variants could be biased. More robust efficacy by variant (on the complete cohort) are awaited for the double-blind (and open label) phase.

Subgroup Analysis COV3001 and COV3009:

In general, subgroup analyses of the final analysis data of COV3001 suggest consistency of efficacy results across age categories and in those with and without comorbidities. Despite lower number of cases, there is much less variability in the efficacy estimates for severe COVID-19 compared to symptomatic COVID-19. Subgroup analyses across age categories, for participants with/without comorbidities, and according to region show fairly similar point estimates. The subgroup analyses do not raise concern of lack of efficacy for particular subgroups in COV3009, but estimates were very imprecise.

In COV3001, efficacy was much higher in the US compared to Latin America and South Africa. In the US, VE against moderate/severe COVID-19 was 73% for cases with onset at least 28 days after vaccination. The FU period is very short in the US, and unblinding occurred earlier. Most cases were captured early. The reference variant was overrepresented in the US compared to other countries and the most important driving factor of VE is the type of variant. In COV3009, large regional differences in terms of efficacy were observed as well. In the US, VE (95% CI) against moderate/severe COVID-19 at least 14 days after the booster dose (second dose) was 93.7% (58.45; 99.85). In the US, the predominant variant during the study was the Alpha. Observed VE in other regions was lower (60.0%-68.8%), which was possibly driven by reduced VE against certain SARS-CoV-2 variants.

FU period in COV3001 and COV3009:

In both studies, the enrolment period and follow up duration varied across countries, and according to baseline characteristics. This is because: (i) Enrolment started at different time across countries (first in the US, with other countries following later at various periods), (ii) Safety pauses occurred at different time across countries, (iii) Per study design, elderly participants and participants with comorbidities were

enrolled later, (iv) Calendar time at unblinding and cross-vaccination differed across the countries (was earlier in the US) and age categories (was earlier in the elderly). In addition, the baseline characteristics and the variants circulation pattern varied across countries and over calendar time. This has an important impact on the person-years of follow-up in some subgroups, such as the elderly. There are also differences in terms of vaccination periods across countries and subgroups. It is not clear at this stage how this could have impacted the efficacy estimates in the subgroups, and across variants.

Vaccine Efficacy against Asymptomatic SARS-CoV-2 Infections in COV3001 and COV3009:

Undetected/asymptomatic COVID-19 cases were ascertained either based on serologic testing (seroconversion to the SARS-COV-2 Nucleoprotein ELISA assay) and/or a positive PCR (based on 'accidental' detection of asymptomatic cases) in the absence of COVID-19 signs and symptoms. In practice, the majority were detected by seroconversion, as serologic testing was done in all participants at regular timepoints. The efficacy (95% CI) against asymptomatic SARS-CoV-2 infection was 28.9% (19.99; 36.78) after a single dose and 34.2% (-6.44; 59.78) after two doses, respectively in COV3001 and COV3009. Therefore efficacy is lacking for asymptomatic cases, whether after a single dose or after two doses of Ad26.COV2.S.

Efficacy conclusion:

Results of the final analysis up to the end of the double-blind phase are presented for the COV3001 (median FU of approximately 4 months, cut-off date 9 July 2021). The MAH also presents preliminary results of the primary/final analysis of the double-blind phase of the COV3009 (median FU of 36 days, cut-off date 25 June 2021). The trials assess respectively a single- and a 2-dose schedule two months apart vs placebo. None of the trials was designed to assess superiority of the two-dose schedule over the single dose schedule, or to make any direct comparison between a two-dose and a single-dose schedule. Based on the available data, it is not possible to make robust conclusion on the benefit of a booster dose given at least 2 months after a single dose of Ad26.COV2.

Study **COV3001** assessed a single dose of Ad26.COV2.S in multiple countries (US, several countries in Latin America, South Africa). There was a high diversity of variants amongst cases, without a dominant variant. A different pattern was observed with respect to efficacy depending on the endpoint.

For symptomatic COVID-19, efficacy was poor over the approximately 6 months FU period. The estimates were 67% (95% CI: 59.0; 73.4) and 56% (95% CI: 51.3; 60.8) respectively in the primary (median FU 2 months) and final (median FU 4 months) analyses. A drop of efficacy was observed rapidly (just a few weeks following vaccination), in parallel with the progressive disappearance of the reference strain and emergence of several variants. Although it is not possible to firmly disentangle the role of waning of protective immunity from the role of variants, the observed drop is considered more likely mainly due to emergence of variants with low/lacking efficacy. Waning of protective immunity over time might also contribute. Efficacy against symptomatic COVID-19 was good for the reference strain and Alpha variant but very poor/lacking for other variants (Beta, Gamma, Mu, Lambda). Only very limited data are available for the Delta variant and those point to a signal of lack of efficacy.

For severe COVID-19, no drop of efficacy was observed up to 6 months following a single dose of Ad26.COV2.S. Efficacy was maintained at 73% (95% CI: 63.9; 80.5) in the final analysis, despite the emergence of diverse variants. At the primary analysis, the efficacy against severe disease was 77% (95% CI: 54.6; 89.1). There was less variability in terms of efficacy across the variants for severe COVID-19 (compared to symptomatic COVID-19), with efficacy point estimates maintained over 60% for the variants for which sufficient data were available (Beta, Gamma, Mu). Still efficacy was higher for the reference strain (around 90%).

Study **COV3009** assessed a two-dose schedule given 56 days apart vs placebo in multiple countries (US, several countries in Europe and in Latin America, South Africa, Philippines). Alpha and Mu were the two dominant variants.

Efficacy of two doses of Ad26.COV2.S administered two months apart was 75% (95% CI: 54.6; 87.3) against symptomatic COVID-19 over a median FU period of 36 days. Therefore, the point estimate was numerically higher compared to the estimate in trial COV3001 assessing a single dose, but CI widely overlap. The VE estimate against Alpha variant is higher in COV3009 compared to the estimate in COV3001 (with widely overlapping CIs). Efficacy was not demonstrated for other variants in COV3009.

The data across trials thus suggest that a booster dose (second dose) at 2 months could provide additional protection against symptomatic COVID-19, but do not suggest a major added value.

Beside the limitations associated with comparing data across trials, several important limitations have been identified in trial COV3009. Given the huge discrepancy between the FAS and the PP (approximately half of the subjects were excluded from the PP set), the analysis cannot be considered as resulting from a randomized comparison. The very short time of FU (36 days PD2) (due to unblinding and cross-vaccination) also considerably limits the interpretation of the results of COV3009. There are very limited data on severe cases and in elderly for the two dose schedule. Importantly there are limited data by SARS-CoV-2 variants, and very limited data on the currently most relevant variant which is the Delta. In addition, spike sequence data were available for only 68% of the cases with an imbalance across arms, possibly leading to biases. Follow up period varied across countries, and variants distribution evolved over time and differed across countries, which could also lead to biases when estimating efficacy by variants. All these issues raise concern on the robustness of the findings of COV3009, especially for the variants.

Overall, the available data across clinical trials suggests that a booster dose (second dose) administered 2 months after the first might provide additional protection against symptomatic COVID-19 including for variants, but do not suggest a major added value.

5. Clinical Safety aspects

5.1. Introduction

Submitted data include data from participants who either received a primary dose and a booster of Ad26.COV2.S at the 5×10^{10} vp dose level, or 2 doses of Ad26.COV2.S at the 1×10^{11} dose level with a 2- or 3-month interval, or a primary dose of 5×10^{10} vp Ad26.COV2.S followed by an 1.25×10^{10} vp Ad26.COV2.S booster 6 months later (considered supportive data) (COV1001, COV1002, COV2001 and COV3009). Preliminary safety data of an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) administered at least 6 months after primary single-dose Ad26.COV2.S (5×10^{10} vp) vaccination are also presented (dose-level blinded data of study COV2008).

The results of the safety analysis for the double-blind phase of COV3009 are discussed here.

Updated safety clinical data has also been submitted for study COV3001 after 1 dose of Ad26.COV2.S 5×10^{10} vp. Safety data from COV3001 was the main data for initial assessment of conditional MA.

Table 16 provides an overview of the number of participants who have received 2 doses of Ad26.COV2.S in studies COV1001, COV1002, COV2001 and COV3009, by dose level and vaccination interval. It also includes numbers for those participants who have received an Ad26.COV2.S booster in study COV2008.

A total of 9,379 participants received a primary dose and a booster of Ad26.COV2.S at the 5×10^{10} vp dose level: 9,073 with a 2-month interval across studies COV1001, COV1002, COV2001, and COV3009; 128 with a 3-month interval across studies COV1001 and COV2001; 19 with a 6-month interval in study COV1001; An estimated 159 with a ⩾6-month interval in study COV2008 (dose-level blinded data).

Across studies COV1001 and COV1002, 235 participants received 2 doses of 1×10^{11} vp Ad26.COV2.S with a 2- or 3-month interval. Furthermore, 74 participants received a primary dose of 5×10^{10} vp Ad26.COV2.S followed by 1.25×10^{10} vp Ad26.COV2.S booster 6 months later in COV2001.

In study COV2008, preliminary dose level-blinded safety data are available from a total of 370 participants (including 7-day reactogenicity data from 244 participants), who have received an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) at least 6 months after primary single-dose Ad26.COV2.S (5×10^{10} vp) vaccination (i.e. in COV3001). Dose level-blinded reactogenicity data are also available from 161 participants (including 7-day reactogenicity data from 76 participants) who have received an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) at least 6 months after primary (2-dose) administration of Pfizer's BNT162b2.

Table 16: Number of Adult Participants who Received a Second or Booster Dose of Ad26.COV2.S by Dose Level and Vaccination Interval (COV1001, COV1002, COV2001, COV2008 and COV3009)

	Data with 2 doses at the 5×10^{10} vp dose level				Supportive data (other dose levels)			Preliminary data[a]		Additional data	
	2-month interval 5×10^{10} vp, 5×10^{10} vp	3-month interval 5×10^{10} vp, 5×10^{10} vp	6-month interval 5×10^{10} vp, 5×10^{10} vp	≥6-month interval 5×10^{10} vp, 5×10^{10}	2-month interval 1×10^{11} vp, 1×10^{11} vp	3-month interval 1×10^{11} vp, 1×10^{11} vp	6-month interval 5×10^{10} vp, 1.25×10^{10} vp	≥6-month interval 5×10^{10} vp, 2.5×10^{10} or 1×10^{10} vp	≥6-month interval BNT162b2, 5×10^{10} or 2.5×10^{10} or 1×10^{10} vp	6-month interval 1×10^{11} vp, 1.25×10^{10} vp	2-month interval 2.5×10^{10} vp, 2.5×10^{10} vp or 1.25×10^{10} vp, 1.25×10^{10} vp
COV1001	190 [c]	77 [b]	19	0	79	80 [b]	0	0	0	0	0
COV1002	91	0	0	0	76	0	0	0	0	0	0
COV2001	137 [d]	51	0	0	0	0	74	0	0	68	147
COV2008	0	0	0	159[a]	0	0	0	211[a]	161	0	0
COV3009	8,655	0	0	0	0	0	0	0	0	0	0
Total	**9,073**	**128**	**19**	**159**	**155**	**80**	**74**	**211**	**161**	**68**	**147**
	9,379				**309**						

Cut-off dates were 21 July 2021 for COV1001, 28 December 2020 for Cohort 1 of COV1002, 22 February 2021 (disposition, demographics, and solicited AEs) and 02 August 2021 (unsolicited AEs and SAEs) for Cohort 2 of COV1002, 11 May 2021 for COV2001, and 25 June 2021 for COV3009. For COV2008, data were extracted from the database on 7 September 2021.

A 3-month vaccination interval corresponds with an 84-day interval per protocol; a 2-month vaccination interval corresponds with a 56-day interval per protocol.

Numbers indicate number of participants who have completed the full vaccination regimen as described in the table header (ie, participants that had only received Dose 1 at the time of the cut-off are not included).

[a] Dataset only includes dose-level blinded safety data. Based on the randomization ratio, for the 370 participants who initially received a primary dose of Ad26.COV2.S (5×10^{10} vp), approximately 52 participants received a 1×10^{10} vp booster, approximately 159 received a 2.5×10^{10} vp booster, and approximately 159 received a 5×10^{10} vp booster. For the 161 participants who initially received a primary 2-dose regimen of Pfizer's BNT162b2, approximately 23 participants received a 1×10^{10} vp booster, approximately 69 received a 2.5×10^{10} vp booster, and approximately 69 received a 5×10^{10} vp booster. Preliminary dose-level blinded heterologous safety data are not discussed in this Clinical Overview Addendum.

[b] Cohort 3 (Group 1 and 3) had a 2-month interval planned per protocol; however, due to a study pause all 157 participants except 3 sentinel participants per group received their second dose after 3 months.

[c] Includes 15 participants from Cohort 2b (Group 2) who have received an Ad26.COV2.S booster (5×10^{10} vp) 8 months post-dose 1.

[d] COV2001 Group 7 had a 1-month interval planned per protocol; however, due to a study pause participants received their second dose at 2 months.

Sources:

- COV1001: Appendix 2 Table 21, Table 23, Table 25, Table 27, Table 29
- COV1002: Appendix 3 Table 63, Table 65
- COV2001: Appendix 4 Table 73
- COV2008: Appendix 5 Table 93, Table 94, Table 100, Table 101
- COV3009: Appendix 8 Table 134

f. Considered supportive data for the 2-dose safety analysis included in this Clinical Overview Addendum.
g. Alternative multiple-dose vaccination regimens that are not discussed in this Clinical Overview Addendum.
h. Includes 15 participants from Cohort 2b (Group 2) who have received an Ad26.COV2.S booster (5×10^{10} vp) 8 months post-dose 1.
i. Cohort 3 (Group 1 and 3) had a 2-month interval planned per protocol; however, due to a study pause all 157 participants except 3 sentinel participants per group received their second dose after 3 months.
j. COV2001 Groups 7 and 8 had a 1-month interval planned per protocol; however, due to a study pause participants received their second dose at 2 months.
k. Includes 244 participants for whom 7-day reactogenicity data are available.
l. Includes 76 participants for whom 7-day reactogenicity data are available.
m. COV2008 includes participants who received a single-dose (5×10^{10} vp) Ad26.COV2.S vaccination in study COV3001 and participants who completed primary vaccination with a 2-dose regimen of Pfizer's BNT162b2 vaccine prior to enrollment in study COV2008. Participants will then receive an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) ≥6 months after primary vaccination in study COV2008.

Sources:
- COV1001: Appendix 2 Table 21, Table 23, Table 25, Table 27, Table 29
- COV1002: Appendix 3 Table 63, Table 65
- COV2001: Appendix 4 Table 73
- COV2008: Appendix 5 Table 93, Table 94, Table 100, Table 101
- COV3009: Appendix 8 Table 134, Table 136

Clinical data from DMID 21-0012 study, cohort 1, groups 4E, 5E and 6E were also submitted: homologous or heterologous booster vaccination with Ad26.COV2.S 5×10^{10} vp at least 12 weeks after primary vaccination with an approved mRNA COVID-19 vaccine regimen (2 doses of Moderna-mRNA-1273 or Pfizer/BioNTech-BNT162b2) or Ad26.COV2.S 5×10^{10} vp.

5.2. Overall Methods

Overall, adverse events (AEs) are being collected as summarized below:

- Solicited local (injection site pain/tenderness, erythema, induration (COV1002 only), and swelling), and systemic AEs (reactogenicity: fatigue, headache, nausea, myalgia, and pyrexia/fever (body temperature ⩾38° C/100.4° F) from the day of vaccination until 7 days after each vaccination). Solicited local AEs were considered as related to the study vaccine by definition. Solicited systemic and unsolicited AEs were considered related to the use of the study vaccine as per investigator assessment.
- Unsolicited AEs from the day of vaccination until 28 days after each vaccination.
- All SAEs, including deaths, and AEs leading to study/vaccine discontinuation from the day of first vaccination until the end of the study. Any respiratory tract infection fulfilling the criteria of an SAE was reported as such during the studies. If the molecular test was positive for SARS-CoV-2, the SAE was excluded from the SAE analysis.
- Adverse events of special interest (AESIs): suspected AESIs were collected from the day of vaccination until the end of the study/early withdrawal. At the time of initial protocol writing for COV1001, COV1002, COV2001 and COV3009, no AESIs were specified for Ad26.COV2.S clinical development. In April 2021, the Ad26.COV2.S clinical program was paused to evaluate a safety concern of thrombosis with thrombocytopenia syndrome (TTS), which was identified through post-marketing data. At this time, all study protocols were amended to include TTS as an AESI.
- Adverse events of interest: AEs of interest were selected for further evaluation during the course of the clinical development, representing various diseases and conditions including, but not limited to severe allergic reactions (eg, hypersensitivity reactions and anaphylaxis), immune-mediated and (neuro)inflammatory events (eg, Guillain-Barré Syndrome (GBS), Bell's palsy).

For studies COV1001, COV1002, COV2001, and COV2008, safety analyses were conducted on the FAS, which includes all participants who received at least 1 dose of the study vaccine (ie, active vaccine or control/placebo). For studies COV3001 and COV3009, the analysis of the double-blind phase of each study includes data from the Safety Subset (ie, a subset of the FAS) for the analysis of solicited and unsolicited AEs, and data from the FAS for the analysis of MAAEs, deaths, other SAEs and AEs leading to study/vaccine discontinuation.

For study DMID21-0012, AEs were collected as follows: solicited local and systemic AEs for 7 days following the booster dose; unsolicited AEs from dose 1 to 28 days following each booster dose; MAAEs, SAEs, new onsets chronic medical conditions (NOCMCs), and AEs of interest from dose 1 to 12 months post last dose on study.

Of note, for potential TTS cases, the criteria for classification agreed by PRAC in the context of the Monthly summary safety review of COVID-19 Vaccine Janssen are the following:

Confirmed	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL +	Anti-PF4 Abs
Probable	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL	
Possible	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L OR wording compatible with platelet count decreased		
Unlikely	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event			
Criteria Not met	One or none of the criteria are met			

5.3. Study COV1001

5.3.1. Methods

This is an ongoing randomized, double-blind, placebo-controlled, FIH Phase 1/2a multicenter study in adults aged 18 to 55 years and 65 years or older. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S are being evaluated at 2 dose levels, administered IM as a single dose or 2-dose schedule, with a single booster vaccination at 6, 12 or 24 months after the primary vaccination regimen administered in Cohort 2. The planned total sample size was approximately 1,045 participants.

Topline results (TLR) have been submitted (data cutoff: 21 July 2021).

In each cohort, after the 1st dose, the median follow-up is between 223 and 268 days. After the 2nd dose at D57 (cohorts 1a, 1b and 2b), the median follow-up is between 167 and 203 days. After the 2nd dose at D85 (cohort 3), the median follow-up is 144 days. After the 2nd dose at 6 months (cohort 2a), the median follow-up is 41 days.

5.3.2. Results

5.3.2.1. Cohort 1a (Adults Aged 18 to 55 Years)

Group 1 data (D1 and D57 vaccinations with 5.10^{10} vp) are of main interest (N=77 1st dose, N=74 2nd dose). Group 3 data (D1 and D57 vaccination with 1.10^{11} vp) are supportive (N=75 1st dose, N=74 2nd dose). The other groups are of less interest for the purpose of this variation.

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen				Injection 3	Booster Vaccination					
				Day 1 (Vac 1)	Day 29 (Vac 2)	Day 57 (Vac 2)	Day 85 (Vac 2)	4 Months post-dose 2	6 months post-dose 1	8 months post-dose 1	12 months post-dose 1	14 months post-dose 1	24 months post-dose 1	26 months post-dose 1
Study COV1001[c]														
Cohort 1a (Adults ≥18 to ≤55 years)														
Group 1[d]	75	77	74	5×10^{10} vp	-	5×10^{10} vp	-							
Group 2	75	75	-	5×10^{10} vp	-	Placebo	-							
Group 3[d]	75	75	74	1×10^{11} vp	-	1×10^{11} vp	-	-	-					
Group 4	75	73	-	1×10^{11} vp	-	Placebo	-							
Group 5	75	77	-	Placebo	-	Placebo	-							

5.3.2.1.1. Demographic and baseline characteristics

Most of the 377 participants were white (91%), 52.5% were female and 47.5% were male. The median age was 34 years (range: 18-55 years) and the median BMI was 24.5 kg/m^2 (range: 17-30 kg/m^2). These characteristics were similar in each group. The small number of SARS-CoV-2 seropositive participants at baseline (3 participants in group 1, and 2 participants in group 3) precluded any meaningful conclusion to be drawn for this subgroup.

Post-dose 1, the intake of concomitant medication of special interest was lower in groups 1 (35.1%) and 2 (33.3%) (i.e. vaccinations with 5.10^{10} vp) compared to groups 3 (60%) and 4 (56.2%) (i.e. vaccinations with 1.10^{11} vp); difference mainly driven by the intake of paracetamol and ibuprofen. In group 5 (placebo), the intake was only of 6.5%.

Post-dose 2, the intake of concomitant medication of special interest was also lower in group 1 (17.6%) (i.e. vaccinations with 5.10^{10} vp) compared to group 3 (39.2%) (i.e. vaccinations with 1.10^{11} vp).

The intake of concomitant medication was highest post-dose 1 compared to post-dose 2 for the 2 tested doses.

5.3.2.1.2. Solicited AEs

In group 1, the frequency of solicited AEs was similar after the 1st (75.3%) and the 2nd dose (77%) of 5x10^{10} vp Ad26.COV2.S (2 months apart). The frequency of solicited AEs ≥ grade 3 was higher after the 1st dose (9.1%) compared to the 2nd dose (1.4%) (all systemic). The frequencies of solicited local AEs and solicited systemic AEs were similar after the 1st dose (64.9% and 62.3%, respectively) and the 2nd (66.2% and 58.1%, respectively). There were no solicited local AEs ≥ grade 3.

In group 3, the frequency of solicited AEs was higher after the 1st (90.7%) compared to the 2nd dose (81.1%) of 1x10^{11} vp Ad26.COV2.S (2 months apart), mainly due to the difference observed for the solicited systemic AEs (84% 1st dose vs. 68.9% 2nd dose). The frequency of solicited AEs ≥ grade 3 was higher after the 1st dose (16%) compared to the 2nd dose (8.1%) (mainly systemic). The frequencies of solicited local AEs were similar after the 1st dose (76%) and the 2nd (74.3%).

In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In groups 1 and 3, the most frequently reported solicited local AE was vaccination site pain, with a frequency similar post-dose 1 (64.9% and 76%, respectively) and post-dose 2 (66.2% and 74.3%, respectively) (mainly grade 1 and 2). A trend towards a decrease in the frequency and severity of

solicited local AEs with increasing age of participants was observed in all active vaccine groups post any Ad26.COV2.S administration.

Solicited systemic AEs

In group 1, the most frequently reported solicited systemic AE, fatigue, was reported with similar frequency post-dose 1 (46.8%) and post-dose 2 (48.6%). However, all other solicited systemic AEs were reported more frequently post-dose 1 compared to post-dose 2: headache (44.2% vs. 33.8%, respectively), myalgia (37.7% vs. 25.7%), nausea (22.1% vs. 6.8%) and pyrexia (14.3% vs. 4.1%).

In group 3, all solicited systemic AEs were reported more frequently post-dose 1 compared to post-dose 2: fatigue (70.7% vs 48.6%), headache (60% vs. 45.9%, respectively), myalgia (58.7% vs. 44.6%), nausea (22.7% vs. 16.2%) and pyrexia (38.7% vs. 18.9%).

A trend towards a decrease in the frequency and severity of systemic solicited AEs with increasing age of participants was observed in all active vaccine groups post any Ad26.COV2.S administration.

5.3.2.1.3. Unsolicited AEs

In group 1, the frequency of unsolicited AEs was similar after the 1st (14.3%) and the 2nd dose (13.5%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart). The frequency of unsolicited AEs ≥ grade 3 was higher after the 1st dose (1.3%: 1 hypotensive crisis) compared to the 2nd dose (0%). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (9.1%) compared to the 2nd dose (4.1%). There were no SAE or fatal AE.

In group 3, the frequency of unsolicited AEs was higher after the 1st (34.7%) compared to the 2nd dose (9.5%) of $1x10^{11}$ vp Ad26.COV2.S (2 months apart). The frequency of unsolicited AEs ≥ grade 3 was higher after the 1st dose (5.3%) compared to the 2nd dose (0%). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (24%) compared to the 2nd dose (5.4%). There were no fatal AE, but 1 SAE post-dose 1 (blood pressure decreased – not related to vaccine).

Only chills was reported with a frequency of at least 10% in any group (15.1% in group 4, post-dose 1 after $1x10^{11}$ vp Ad26.COV2.S). Post-dose 1, chills was reported with a frequency of 3.9% in group 1 ($5x10^{10}$ vp) and 6.7% in group 3 ($1x10^{11}$ vp).

In group 1, the unsolicited AE assessed as related to vaccination were the following post-dose 1: chills (3.9%), pyrexia (1.3%), vaccination site swelling (1.3%), back pain (2.6%), hyperhidrosis (1.3%), sensitive skin (1.3%), diarrhoea (1.3%), eye irritation (1.3%), ocular discomfort (1.3%), oropharyngeal pain (1.3%) and hypotensive crisis (1.3%). Post-dose 2, there were: pyrexia (1.4%), back pain (1.4%), and headache (1.4%).

5.3.2.2. Cohort 1b (Adults Aged 18 to 55 Years)

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen				Injection 3	Booster Vaccination					
				Day 1 (Vac 1)	Day 29 (Vac 2)	Day 57 (Vac 2)	Day 85 (Vac 2)	4 Months post-dose 2	6 months post-dose 1	8 months post-dose 1	12 months post-dose 1	14 months post-dose 1	24 months post-dose 1	26 months post-dose 1
Study COV1001[c]														

Cohort 1b (Adults ≥18 to ≤55 years)									
Group 1[f]	5	5	4	5×10^{10} vp	-	5×10^{10} vp	-		
Group 2	5	5	-	5×10^{10} vp	-	Placebo	-		
Group 3[f]	5	5	5	1×10^{11} vp	-	1×10^{11} vp	-	-	-
Group 4	5	5	-	1×10^{11} vp	-	Placebo	-		
Group 5	5	5	-	Placebo	-	Placebo	-		

Cohort 1b comprised 5 participants in each group who were enrolled at Beth Israel Deaconess Medical Center (BIDMC) and for whom additional exploratory immunogenicity analyses were performed.

Group 1 data (D1 and D57 vaccinations with 5.10^{10} vp) are of main interest. However, because of the number of subjects per group (N=5 1st dose, N=4 2nd dose), the relevance is very limited. Group 3 data (D1 and D57 vaccination with 1.10^{11} vp) are supportive (N=5 1st dose, N=5 2nd dose). The other groups are of less interest for the purpose of this variation.

5.3.2.2.1. Demographic and baseline characteristics

Most of the 25 participants were white (88%), 56% were female and 44% were male. The median age was 42 years (range: 22-52 years) and the median BMI was 24.8 kg/m^2 (range: 19-30 kg/m^2). There were no SARS-CoV-2 seropositive participants at baseline in groups 1 and 3.

Post-dose 1, the intake of concomitant medication of special interest was lower in groups 1 (40%) and 2 (60%) (i.e. vaccinations with 5.10^{10} vp) compared to groups 3 (100%) and 4 (80%) (i.e. vaccinations with 1.10^{11} vp); difference mainly driven by the intake of paracetamol and ibuprofen. In group 5 (placebo), the intake was of 40%.

Post-dose 2, the intake of concomitant medication of special interest was also lower in group 1 (50%) (i.e. vaccinations with 5.10^{10} vp) compared to group 3 (80%) (i.e. vaccinations with 1.10^{11} vp).

5.3.2.2.2. Solicited AEs

In group 1, the frequency of solicited AEs was similar after the 1st (80%) and the 2nd dose (100%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (no AEs ≥ grade 3). The frequencies of solicited local AEs and solicited systemic AEs were similar after the 1st dose (80% and 80%, respectively) and the 2nd (100% and 75%, respectively).

In group 3, the frequency of solicited AEs was similar after the 1st (100%) and the 2nd dose (100%) of $1x10^{11}$ vp Ad26.COV2.S (2 months apart). The frequencies of solicited local AEs and solicited systemic AEs were similar after the 1st dose (100% and 100%, respectively) and the 2nd (100% and 80%, respectively). The frequency of solicited AEs ≥ grade 3 was higher after the 1st dose (60%) (all systemic) compared to the 2nd dose (0%).

In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In groups 1 and 3, the most frequently reported solicited local AE was vaccination site pain, with a frequency similar post-dose 1 (80% and 100%, respectively) and post-dose 2 (100% and 100%, respectively) (mainly grade 1 and 2).

Solicited systemic AEs

In group 1, fatigue was reported less frequently post-dose 1 (40%) compared to post-dose 2 (75%). However, all other solicited systemic AEs were reported more frequently (or similarly) post-dose 1 compared to post-dose 2: headache (40% vs. 25%, respectively), myalgia (40% vs. 25%) and nausea (20% vs. 25%) (no pyrexia).

In group 3, all solicited systemic AEs were reported more frequently post-dose 1 compared to post-dose 2: fatigue (100% vs 60%), headache (100% vs. 80%, respectively), myalgia (100% vs. 40%), nausea (60% vs. 0%) and pyrexia (60% vs. 20%).

5.3.2.2.3. Unsolicited AEs

In group 1, the frequency of unsolicited AEs was similar after the 1st (40%) and the 2nd dose (50%) of 5x10^{10} vp Ad26.COV2.S (2 months apart) (all grade 1). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (20%) compared to the 2nd dose (0%). There were no fatal AE, but 1 SAE post-dose 1 (Nephrolithiasis - not related to vaccine).

In group 3, the frequency of unsolicited AEs was higher after the 1st (80%) (all grade 2) compared to the 2nd dose (20%) (grade 1) of 1x10^{11} vp Ad26.COV2.S (2 months apart). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (60%) compared to the 2nd dose (0%). There were no SAE or fatal AE.

In group 1, no unsolicited AEs were reported twice (and only 1 injection site haemorrhage reported post-dose 1 was assessed as related to vaccine). In group 2, the most frequently reported unsolicited AE was chills with an highest frequency post-dose 1 (80%; all considered related to vaccine) compared to post-dose 2 (none).

5.3.2.3. Cohort 2a (Adults Aged ≥18 to ≤55 Years)

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen: Day 1 (Vac 1)	Primary Regimen: Day 29 (Vac 2)	Primary Regimen: Day 57 (Vac 2)	Primary Regimen: Day 85 (Vac 2)	Injection 3: 4 Months post-dose 2	Booster Vaccination: 6 months post-dose 1	Booster Vaccination: 8 months post-dose 1	Booster Vaccination: 12 months post-dose 1	Booster Vaccination: 14 months post-dose 1	Booster Vaccination: 24 months post-dose 1	Booster Vaccination: 26 months post-dose 1
Study COV1001[c]														
Cohort 2a (Adults ≥18 to ≤55 years)														
Group 2[c]	30	29	19	5×10^{10} vp	-	-	-		5×10^{10} vp	-	Placebo	-	Placebo	-
Group 1	30			5×10^{10} vp	-	-	-		Placebo	-	Placebo	-	Placebo	-
Group 3	30	90	-	5×10^{10} vp	-	-	-	-	Placebo	-	5×10^{10} vp	-	Placebo	-
Group 4	30			5×10^{10} vp	-	-	-		Placebo	-	Placebo	-	5×10^{10} vp	-
Group 5	15	17	-	Placebo	-	-	-		Placebo	-	Placebo	-	Placebo	-

Group 2 data (D1 vaccination and booster dose at 6 month with 5.10^{10} vp) are of main interest, however the number of subjects is limited (N=29 1st dose, N=19 2nd dose). The other groups are of less interest for the purpose of this variation.

5.3.2.3.1. Demographic and baseline characteristics

Most of the 136 participants were white (83.8%), 51.5% were female and 48.5% were male. The median age was 37 years (range: 19-55 years) and the median BMI was 24.4 kg/m^2 (range: 17-30 kg/m^2). These characteristics were similar in each group. The small number of SARS-CoV-2

seropositive participants at baseline (2 participants in group 2 and 5 in groups 1, 3 and 4) precluded any meaningful conclusion to be drawn for this subgroup.

Post-dose 1, the intake of concomitant medication of special interest was similar in group 2 (41.4%) and groups 1, 3 and 4 (47.8%) (i.e. vaccinations with 5.10^{10} vp) (mainly paracetamol and ibuprofen). In group 5 (placebo), the intake was of 29.4%.

In group 2 (i.e. vaccinations with 5.10^{10} vp), the intake of concomitant medication was highest post-dose 1 (41.4%) compared to post-dose 2 (26.3%).

5.3.2.3.2. Solicited AEs

In group 2, the frequency of solicited AEs was higher after the 1st (93.1%) compared to the booster dose (78.9%) of $5x10^{10}$ vp Ad26.COV2.S (6 months apart) (1 headache AE ≥ grade 3 post-dose 1). The frequency of solicited local AEs was similar after the 1st dose (82.8%) and the booster dose (78.9%). The frequency of solicited systemic AEs was higher after the 1st dose (79.3%) compared to the booster dose (57.9%). All solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In group 2, the most frequently reported solicited local AE was vaccination site pain, with a frequency similar post-dose 1 (79.3%) and post-booster dose (78.9%) (grade 1 and 2).

Solicited systemic AEs

In group 2, all solicited systemic AEs were reported more frequently post-dose 1 compared to post-booster dose: fatigue (58.6% vs 26.3%), headache (55.2% vs. 47.4%, respectively), myalgia (58.6% vs. 21.1%), nausea (27.6% vs. 10.5%) and pyrexia (10.3% vs. 0%).

5.3.2.3.3. Unsolicited AEs

In group 2, the frequency of unsolicited AEs was higher after the 1st (17.2%) compared to the booster dose (10.5%) of $5x10^{10}$ vp Ad26.COV2.S (6 months apart) (grade 1 and 2). The frequency of unsolicited AEs considered related to the study vaccine was similar after the 1st dose (6.9%) and the booster dose (5.3%). There were no SAE or fatal AE.

Only fatigue was reported with a frequency of at least 10% in any group (11.8% in group 5, post-dose 1 and post-booster dose (after placebo each). Fatigue was not reported in group 2.

In group 2, post-dose 1, the only unsolicited AE related to vaccination was pyrexia (6.9%). Post-booster dose, 2 unsolicited AE related to vaccination were reported in 1 subject: presyncope and abdominal pain (5.3% each).

5.3.2.4. Cohort 2b (Adults Aged 18 to 55 Years)

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen: Day 1 (Vac 1)	Primary Regimen: Day 29 (Vac 2)	Primary Regimen: Day 57 (Vac 2)	Primary Regimen: Day 85 (Vac 2)	Injection 3: 4 Months post-dose 2	Booster Vaccination: 6 months post-dose 1	Booster Vaccination: 8 months post-dose 1	Booster Vaccination: 12 months post-dose 1	Booster Vaccination: 14 months post-dose 1	Booster Vaccination: 24 months post-dose 1	Booster Vaccination: 26 months post-dose 1
Study COV1001[c]														
Cohort 2b (Adults ≥18 to ≤55 years)														
Group 1[f]	30	120	112[h]	5×10^{10} vp	-	5×10^{10} vp	-	-	-	Placebo	-	Placebo	-	Placebo
Group 2[f]	30			5×10^{10} vp	-	5×10^{10} vp	-		-	5×10^{10} vp	-	Placebo	-	Placebo
Group 3[f]	30			5×10^{10} vp	-	5×10^{10} vp	-		-	Placebo	-	Placebo	-	Placebo
Group 4[f]	30			5×10^{10} vp	-	5×10^{10} vp	-		-	Placebo	-	Placebo	-	5×10^{10} vp
Group 5	15	15	-	Placebo	-	Placebo	-		-	Placebo	-	Placebo	-	Placebo

The following group are of main interest: group 2 (D1, D57 vaccination, and booster dose at 8 months with 5.10^{10} vp) (N=30 1st dose, N=29 2nd dose), and groups 1, 3, and 4 (D1 and D57 vaccination with 5.10^{10} vp, and placebo booster dose at 8 months) (N=90 1st dose, N=83 2nd dose). The last group 5 is of less interest for the purpose of this variation. However, only post-dose 1 and post-dose 2 data are relevant.

5.3.2.4.1. Demographic and baseline characteristics

Most of the 135 participants were white (86.7%), 43% were female and 57% were male. The median age was 37 years (range: 19-55 years) and the median BMI was 24.5 kg/m^2 (range: 18-30 kg/m^2). These characteristics were similar in each group. However, in group 5 (placebo), there were 66.7% females and 33.3% males. The small number of SARS-CoV-2 seropositive participants at baseline (1 participant in group 2 and 2 in groups 1, 3 and 4) precluded any meaningful conclusion to be drawn for this subgroup.

Post-dose 1, the intake of concomitant medication of special interest was similar in group 2 (40%) and groups 1, 3 and 4 (45.6%) (i.e. vaccinations with 5.10^{10} vp) (mainly paracetamol and ibuprofen). In group 5 (placebo), the intake was of 20%.

In group 2 (i.e. vaccinations with 5.10^{10} vp), the intake of concomitant medication was similar post-dose 1 (20%) compared to post-dose 2 (20.7%). However, in groups 1, 3 and 4 (i.e. vaccinations with 5.10^{10} vp), the intake of concomitant medication was highest post-dose 1 (45.6%) compared to post-dose 2 (32.5%).

5.3.2.4.2. Solicited AEs

In group 2, the frequency of solicited AEs was higher after the 1st (83.3%) compared to 2nd dose (75.9%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (3 subjects with AEs ≥ grade 3 post-dose 1, and 3 subjects with AEs ≥ grade 3 post-dose 2 – mainly systemic). The frequency of solicited local AEs was similar after the 1st dose (76.7%) and the 2nd dose (72.4%). The frequency of solicited systemic AEs was higher after the 1st dose (76.7%) compared to the booster dose (58.6%).

In groups 1, 3 and 4, the frequency of solicited AEs was higher after the 1st (91.1%) compared to 2nd dose (83.1%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (11 subjects with AEs ≥ grade 3 post-dose 1, and 3 subjects with AEs ≥ grade 3 post-dose 2 – mainly systemic). The frequency of solicited local AEs was similar after the 1st dose (77.8%) and the 2nd dose (72.3%). The frequency of solicited systemic AEs was higher after the 1st dose (78.9%) compared to the 2nd dose (66.3%).

In all these groups, all solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In group 2, and in groups 1, 3 and 4, the most frequently reported solicited local AE was vaccination site pain, with a frequency similar post-dose 1 (76.7% and 76.7%, respectively) and post-dose 2 (72.4% and 72.3%, respectively) (grade 1 and 2). A trend towards a decrease in the frequency and severity of solicited local AEs with increasing age of participants was observed in all active vaccine groups post any Ad26.COV2.S administration (18-30 year-of-age vs. 31-45 vs. 46-55).

Solicited systemic AEs

In group 2, all solicited systemic AEs were reported more frequently post-dose 1 compared to post-dose 2: fatigue (50% vs 37.9%), headache (60% vs. 41.4%), myalgia (56.7% vs. 34.5%), nausea (16.7% vs. 17.2%) and pyrexia (10% vs. 3.4%).

In groups 1, 3 and 4, all solicited systemic AEs were reported more frequently post-dose 1 compared to post-dose 2: fatigue (64.4% vs 47%), headache (63.3% vs. 49.4%, respectively), myalgia (46.7% vs. 41%), nausea (24.4% vs. 18.1%) and pyrexia (22.2% vs. 8.4%).

5.3.2.4.3. Unsolicited AEs

In group 2, the frequency of unsolicited AEs was higher after the 1st (20%) compared to the 2nd dose (10.3%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (mainly grade 1 and 2). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (10%) compared to the 2nd dose (3.4%). There were fatal AE but 1 SAE considered as not related to the vaccine (anaphylactic shock and uterine prolapse).

In groups 1, 3 and 4, the frequency of unsolicited AEs was similar after the 1st (17.8%) and the 2nd dose (13.3%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (mainly grade 1 and 2). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (14.4%) compared to the 2nd dose (6%). There were no SAE or fatal AE.

The most frequently reported unsolicited AEs were chills (6.7% in group 2 and 4.4% in groups 1, 3 and 4). All those were reported post-dose 1 and assessed as related to the vaccine.

The most frequently reported unsolicited AEs assessed as related to vaccine were:

- Group 2 post-dose 1: chills (6.7%), abnormal dreams (3.3%), decreased appetite (3.3%)
- Group 2 post-dose 2: feeling cold (3.4%)
- Groups 1, 3 and 4 post-dose 1: chills (4.4%) and fatigue (2.2%),
- Groups 1, 3 and 4 post-dose 2: fatigue (2.4%)

5.3.2.5. Cohort 3 (Adults Aged ≥65 Years)

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen				Injection 3	Booster Vaccination					
				Day 1 (Vac 1)	Day 29 (Vac 2)	Day 57 (Vac 2)	Day 85 (Vac 2)	4 Months post-dose 2	6 months post-dose 1	8 months post-dose 1	12 months post-dose 1	14 months post-dose 1	24 months post-dose 1	26 months post-dose 1
Study COV1001[c]														
Cohort 3 (Adults ≥65 years)														
Group 1[G]	75	81	77	5×10^{10} vp	-	5×10^{10} vp	-							
Group 2	75	80	-	5×10^{10} vp	-	Placebo	-							
Group 3[G]	75	82	80	1×10^{11} vp	-	1×10^{11} vp	-	-						
Group 4	75	79	-	1×10^{11} vp	-	Placebo	-							
Group 5	75	81	-	Placebo	-	Placebo	-							

Cohort 3 (groups 1 and 3) had a 2-month interval planned per protocol; however, due to a study pause all 157 participants except 3 sentinel participants per group received their 2nd dose after 3 months.

Group 1 data (D1 and D85 vaccination with 5.10^{10} vp) are of main interest (N=81 1st dose, N=77 2nd dose). Group 3 data (D1 and D85 vaccination with 1.10^{11} vp) are supportive (N=82 1st dose, N=80 2nd dose). The other groups are of less interest for the purpose of this variation.

5.3.2.5.1. Demographic and baseline characteristics

Most of the 403 participants were white (98.3%), 49.9% were female and 50.1% were male. The median age was 69 years (range: 65-88 years) and the median BMI was 25.7 kg/m^2 (range: 17-30 kg/m^2). These characteristics were similar in each group. The small number of SARS-CoV-2 seropositive participants at baseline (2 participants in group 1 and 3 in group 3) precluded any meaningful conclusion to be drawn for this subgroup.

Post-dose 1, the intake of concomitant medication of special interest was lower in groups 1 (22.2%) and 2 (12.5%) (i.e. vaccinations with 5.10^{10} vp) compared to groups 3 (31.7%) and 4 (27.8%) (i.e. vaccinations with 1.10^{11} vp); difference mainly driven by the intake of paracetamol and ibuprofen. In group 5 (placebo), the intake was only of 8.6%.

Post-dose 2, the intake of concomitant medication of special interest was also lower in group 1 (18.2%) (i.e. vaccinations with 5.10^{10} vp) compared to group 3 (26.3%) (i.e. vaccinations with 1.10^{11} vp).

The intake of concomitant medication was slightly highest post-dose 1 compared to post-dose 2 for the 2 tested doses.

5.3.2.5.2. Solicited AEs

In group 1, the frequency of solicited AEs was similar after the 1st (63%) and the 2nd dose (67.5%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart). The frequencies of solicited local AEs were slightly lower after the 1st dose (46.9%) compared to the 2nd (53.2%). The frequencies of solicited systemic AEs were slightly higher after the 1st dose (48.1%) and the 2nd (42.9%). There were only 1 solicited (systemic) AEs ≥ grade 3 (post-dose 2).

In group 3, the frequency of solicited AEs was similar after the 1st (70.7%) and the 2nd dose (73.8%) of $1x10^{11}$ vp Ad26.COV2.S (2 months apart). The frequencies of solicited local AEs were lower after the 1st dose (40.2%) compared to the 2nd (63.8%). The frequencies of solicited systemic AEs were similar

after the 1st dose (57.3%) and the 2nd (50%). There were only 2 solicited (systemic) AEs ≥ grade 3 post-dose 1, and 1 solicited (systemic) AEs ≥ grade 3 post-dose 2.

In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In groups 1 and 3, the most frequently reported solicited local AE was vaccination site pain, with a frequency lower post-dose 1 (46.9% and 39%, respectively) compared to post-dose 2 (53.2% and 63.8%, respectively) (mainly grade 1 and 2).

Solicited systemic AEs

In group 1, all solicited systemic AEs were reported with similar frequency post-dose 1 compared to post-dose 2: fatigue (32.1% vs 29.9%), headache (28.4% vs. 26%), myalgia (21% vs. 22.1%), nausea (4.9% vs. 1.3%) and pyrexia (4.9% vs. 1.3%).

In group 3, all solicited systemic AEs were reported with similar frequency post-dose 1 compared to post-dose 2: fatigue (36.6% vs 36.3%), headache (37.8% vs. 33.8%), myalgia (26.8% vs. 21.3%), nausea (8.5% vs. 5%) and pyrexia (7.3% vs. 2.5%).

5.3.2.5.3. Unsolicited AEs

In group 1, the frequency of unsolicited AEs was slightly higher after the 1st (19.8%) compared to the 2nd dose (14.3%) of $5x10^{10}$ vp Ad26.COV2.S (3 months apart). The frequency of unsolicited AEs ≥ grade 3 was higher after the 1st dose (3.7%) compared to the 2nd dose (1.3%). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (6.2%) compared to the 2nd dose (0%). There were no fatal AE, but 2 subjects with SAEs not considered as related to vaccine (atrial fibrillation; hip fracture).

In group 3, the frequency of unsolicited AEs was higher after the 1st (23.2%) compared to the 2nd dose (15%) of $1x10^{11}$ vp Ad26.COV2.S (3 months apart). The frequency of unsolicited AEs ≥ grade 3 was higher after the 1st dose (3.7%) compared to the 2nd dose (1.3%). The frequency of unsolicited AEs considered related to the study vaccine was higher after the 1st dose (8.5%) compared to the 2nd dose (3.8%). There were no fatal AE, but 2 subjects with SAEs not considered as related to vaccine (coronary artery disease; uterine prolapse).

In group 1, the most frequently reported unsolicited AEs were hypertension (2.5%), systolic hypertension (2.5%), and bradycardia (2.5%). In group 3, the most frequently reported unsolicited AEs were chills (4.9%), arthralgia (3.7%), back pain (3.7%) and headache (3.7%). All those were reported post-dose 1.

The reported unsolicited AEs assessed as related to vaccine were:

- Group 1 post-dose 1: chills (1.2%), vaccination site pain (1.2%), head discomfort (1.2%), arthralgia (1.2%), urticaria (1.2%) and systolic hypertension (1.2%) (none post-dose 2)
- Group 3 post-dose 1: chills (4.9%), injection site haemorrhage (1.2%), headache (1.2%), arthralgia (1.2%), abdominal distension (1.2%)

- Group 3 post-dose 2: chills (2.5%) and myalgia (1.3%)

5.3.2.6. AEs leading to discontinuation

In the groups of interest (in each cohorts), there were no AE leading to permanent stop of vaccination.

Upon request more details about AE leading to discontinuation have been provided as detailed below:

- Two AEs in cohort 1a group 4 (1.10^{11} vp Ad26.COV2.S, placebo, 2 months apart): Grade 1 non-serious AE of COVID-19 9 days post-dose 1 (Ad26.COV2.S $1x10^{11}$ vp) considered not related to the study vaccine; SAE of Grade 3 pyrexia on day of 1st vaccination (Ad26.COV2.S $1x10^{11}$ vp) considered related to the study vaccine.
- One AE in cohort 1b group 1 (5.10^{10} vp Ad26.COV2.S, 5.10^{10} vp Ad26.COV2.S, 2 months apart): SAE of nephrolithiasis (grade 4) reported 46 days post-dose 1 (Ad26.COV2.S 5×10^{10} vp) considered not related to the study vaccine by the investigator and resolved after 20 days.
- One AE in cohort 2a groups 1+3+5 (5.10^{10} vp Ad26.COV2.S, placebo, 2 months apart): same subject reported grade 1 AE of COVID-19 63 days post-dose 1 (Ad26.COV2.S 5×10^{10} vp) (considered not related) and Grade 1 AE of rhinorrhoea 61 days post-dose 1 (considered not related).
- One AE in cohort 2b group 2 (5.10^{10} vp Ad26.COV2.S, 5.10^{10} vp Ad26.COV2.S, 2 months apart, and booster dose at 8 months with 5.10^{10} vp) and one AE in groups 1+3+4 (5.10^{10} vp Ad26.COV2.S, 5.10^{10} vp Ad26.COV2.S, 2 months apart, and placebo at 8 months with 5.10^{10} vp): grade 1 non-serious AE of COVID-19 4 days post-dose 1 (Ad26.COV2.S 5×10^{10} vp) considered not related to the study vaccine; grade 1 non-serious AE of asthma on an unspecified date during post-dose 2 follow-up in the Ad26.COV2.S 5×10^{10} vp, followed by Ad26.COV2.S 5×10^{10} vp group (considered not related).

There was no AE leading to discontinuation in cohort 3.

Overall, there were 2 AEs leading to discontinuation assessed as related to study vaccination: multiple sclerosis (PL, PL group) in Cohort 1a, and grade 3 pyrexia post-dose 1 (1×10^{11} vp, PL group).

5.3.2.7. AESIs

Six participants have been reported with suspected AESIs in this study:

- One participant in the 5×10^{10} vp, booster PL group had thrombocytopenia (not related) in Cohort 2a.
- One participant in the 5×10^{10} vp, 5×10^{10} vp group had transient ischaemic attack (not related) in Cohort 3.
- One participant in the 5×10^{10} vp, PL group had deep vein thrombosis (not related) in Cohort 3.
- In the 1×10^{11} vp, 1×10^{11} vp group, one participant had thrombocytopenia (not related) and other participant had myocardial infarction (not related) in Cohort 3.
- One participant in the 1×10^{11} vp, PL group had deep vein thrombosis (not related) in Cohort 3.

No participant had probable TTS , i.e. both a thromboembolic event and thrombocytopenia.

5.4. Study COV1002

5.4.1. Methods

This is an ongoing randomized, double-blind, placebo-controlled, Phase 1 study in adults aged 20 to 55 years and 65 years and older in Japan. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S are being evaluated at 2 dose levels, administered IM as a 2-dose schedule. The study included the following cohorts:

- Cohort 1: 125 participants, aged 20 to 55 years, were randomized in a 2:2:1 ratio to each dose vaccine group or placebo.
- Cohort 2: 125 participants, aged 65 years or older, were randomized in a 2:2:1 ratio to each dose vaccine group or placebo.

The study duration from screening until the last follow-up visit is approximately 13 months per participant. The study consisted of a screening period of up to 28 days, vaccinations on Days 1 and 57, and follow-up visits up to 1 year after the first vaccination.

An interim CSR has been submitted (data cutoff: 28 December 2020 (Cohort 1 Day 85) and 22 February 2021 (Cohort 2 Day 85)).

An interim safety update report has been also submitted.This report provides updated safety data including unsolicited AEs, deaths, other SAEs and other significant AEs, and narratives for Cohort 1 and Cohort 2 based on snapshot data dated 02 August 2021.

After the 1st dose, the median follow-up is 116 days for cohort 1 (data cutoff: 28 December 2020) and 138 days for cohort 2 (data cutoff: 22 February 2021)). After the 2nd dose at D57, the median follow-up is 59 days for cohort 1 and 81 days for cohort 2.

5.4.2. Results

5.4.2.1. Cohort 1 (Adults Aged 20 to 55 Years)

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen				Injection 3	Booster Vaccination					
				Day 1 (Vac 1)	Day 29 (Vac 2)	Day 57 (Vac 2)	Day 85 (Vac 2)	4 Months post-dose 2	6 months post-dose 1	8 months post-dose 1	12 months post-dose 1	14 months post-dose 1	24 months post-dose 1	26 months post-dose 1
Study COV1002														
Cohort 1 (Adults ≥20 to ≤55 years)														
Group 1[f]	50	51	43	5×10^{10} vp	-	5×10^{10} vp	-	-	-					
Group 2[f]	50	50	31	1×10^{11} vp	-	1×10^{11} vp	-							
Group 3	25	24	-	Placebo	-	Placebo	-							

Group 1 data (D1 and D57 vaccinations with 5.10^{10} vp) are of main interest (N=51 1st dose, N=43 2nd dose). Group 2 data (D1 and D57 vaccination with 1.10^{11} vp) are supportive (N=50 1st dose, N=31 2nd dose). The last group is of less interest for the purpose of this variation.

5.4.2.1.1. Demographic and baseline characteristics

The study was conducted in Japan. Overall, 56.8% of participants were women and 43.2% were men. The median age was 42.0 years (range: 20-55 years), and more than half of the participants (55.2%) were in the age category of 41 to 55 years. The median BMI was 21.8 kg/m^2 (range: 15.3-32.5 kg/m^2). Demographics and baseline characteristics were generally balanced among the vaccine groups. However, in group 3 (placebo), there were 41.7% females and 58.3% males. The small number of SARS-CoV-2 seropositive participants at baseline (2 participants in group 2, and 0 participant each in groups 1 and 3) precluded any meaningful conclusion to be drawn for this subgroup.

Post-dose 1, the intake of concomitant medication of special interest was lower in Group 1 (43.1%) (i.e. vaccinations with 5.10^{10} vp) compared to group 2 (74%) (i.e. vaccinations with 1.10^{11} vp); difference mainly driven by the intake of paracetamol. In group 3 (placebo), the intake was null (table 10 interim CSR).

Post-dose 2, the intake of concomitant medication of special interest was also lower in group 1 (32.6%) (i.e. vaccinations with 5.10^{10} vp) compared to group 2 (45.2%) (i.e. vaccinations with 1.10^{11} vp).

The intake of concomitant medication was highest post-dose 1 compared to post-dose 2 for the 2 tested doses.

5.4.2.1.2. Solicited AEs

In group 1, the frequencies of solicited AEs all grade and ≥ grade 3 (mainly systemic) were higher after the 1st (98% and 7.8%, respectively) compared to the 2nd dose (86% and 2.3%, respectively) of 5x10^{10} vp Ad26.COV2.S (2 months apart). The frequencies of solicited local AEs were similar after the 1st dose (82.4%) and the 2nd (83.7%). The frequencies of solicited systemic AEs were higher after the 1st dose (88.2%) compared to the 2nd (65.1%).

In group 2, the frequencies of solicited AEs all grade and ≥ grade 3 (mainly systemic) were higher after the 1st (98% and 42%, respectively) compared to the 2nd dose (87.1% and 6.5%, respectively) of 1x10^{11} vp Ad26.COV2.S (2 months apart). The frequencies of solicited local and systemic AEs were higher after the 1st dose (86% and 96%, respectively) compared to the 2nd (77.4% and 74.2%, respectively).

In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In group 1, the most frequently reported solicited local AE was vaccination site pain, with a frequency similar post-dose 1 (82.4%) and post-dose 2 (83.7%) (mainly grade 1 and 2). In group 2, the most frequently reported solicited local AE was vaccination site pain, with a frequency highest post-dose 1 (86%) compared to post-dose 2 (77.4%) (mainly grade 1 and 2).

Solicited systemic AEs

In group 1, all solicited systemic AEs were reported with highest frequency post-dose 1 compared to post-dose 2: fatigue (72.5% vs. 46.5%, respectively), headache (52.9% vs. 32.6%, respectively),

myalgia (66.7% vs. 46.5%), nausea (15.7% vs. 11.6%) and pyrexia (25.5% vs. 7%).

In group 2, all solicited systemic AEs were reported with highest frequency post-dose 1 compared to post-dose 2: fatigue (88% vs. 61.3%, respectively), headache (74% vs. 32.3%, respectively), myalgia (74% vs. 45.2%), nausea (14% vs. 12.9%) and pyrexia (74% vs. 32.3%).

5.4.2.1.3. Unsolicited AEs

In group 1, the frequency of unsolicited AEs was similar after the 1st (29.4%) and the 2nd dose (27.9%) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (mainly grade 1). There were no unsolicited AEs ≥ grade 3. The frequency of unsolicited AEs considered related to the study vaccine was similar after the 1st dose (13.7%) and the 2nd dose (14%) (mainly grade 1). There were no fatal AE, but 1 SAE of sudden hearing loss (grade 4) considered unrelated to the vaccine.

In group 2, the frequency of unsolicited AEs was higher after the 1st (42%) compared to the 2nd dose (25.8%) of $1x10^{11}$ vp Ad26.COV2.S (2 months apart) (mainly grade 1). Post-dose 1, there were 2 unsolicited AEs ≥ grade 3 considered related to the vaccine. The frequency of unsolicited AEs considered related to the study vaccine was highest after the 1st dose (36%) compared to the 2nd dose (12.9%). There were no SAE or fatal AE.

In group 1, the most frequently reported unsolicited AEs were:

- Post-dose 1: arthralgia (3.9%), diarrhoea (3.9%) and eczema (3.9%)
- Post-dose 2: diarrhoea (4.7%), administration site pruritus (4.7%), fatigue (4.7%) and headache (4.7%).

In group 1, the reported unsolicited AEs assessed as related to vaccine were:

- Post-dose 1: arthralgia (2%), oropharyngeal discomfort (2%), oropharyngeal pain (2%), fatigue (2%), vaccination site pain (2%), diarrhoea (2%), aphthous ulcer (2%), vertigo (2%), and rash (2%)
- Post-dose 2: arthralgia (2.3%), diarrhoea (2.3%), administration site pruritus (4.7%), chills (2.3%), and rash (2.3%).

For both groups, no new unsolicited AEs (SAE or fatal AE) were reported after the data cut-off date of the interim CSR (28 December 2020) through the data cut-off of the interim safety update report (02 August 2021).

5.4.2.1.4. Clinical laboratory evaluation

The following laboratory abnormalities were reported as AEs (Grade 1 in severity), in any vaccine groups:

- 1/43 (2.3%) participants in the group 1, experienced an AE of C-reactive protein increased post-dose 2, considered not related to the study vaccine.
- 1/43 (2.3%) participants in the group 2, experienced an AE of C-reactive protein increased post-dose 1 follow-up, considered not related to the study vaccine.

- 1/31 (3.2%) participants in the in the group 2 experienced an AE of alanine transferase increased post-dose 2, considered not related to the study vaccine.
- 1/24 (4.2%) participants in the group 3 experienced an AE of C-reactive protein increased post-dose 1, considered not related to the study vaccine.

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, placebo group. Overall, the percentages of participants with abnormal safety laboratory values (biochemistry, hematology, coagulation, and urinalysis) were very low and no notable differences were noted between vaccine and placebo groups and vaccine dose levels.

5.4.2.2. Cohort 2 (Adults Aged 65 Years and older)

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen				Injection 3	Booster Vaccination					
				Day 1 (Vac 1)	Day 29 (Vac 2)	Day 57 (Vac 2)	Day 85 (Vac 2)	4 Months post-dose 2	6 months post-dose 1	8 months post-dose 1	12 months post-dose 1	14 months post-dose 1	24 months post-dose 1	26 months post-dose 1
Study COV1002														
Cohort 2 (Adults ≥65 years)														
Group 1[f]	50	50	48	5×10^{10} vp	-	5×10^{10} vp	-	-	-					
Group 2[f]	50	49	45	1×10^{11} vp	-	1×10^{11} vp	-							
Group 3	25	26	-	Placebo	-	Placebo	-							

Group 1 data (D1 and D57 vaccinations with 5.10^{10} vp) are of main interest (N=50 1st dose, N=48 2nd dose). Group 2 data (D1 and D57 vaccination with 1.10^{11} vp) are supportive (N=50 1st dose, N=45 2nd dose). The last group is of less interest.

5.4.2.2.1. Demographic and baseline characteristics

The study was conducted in Japan. Overall, 50.4% of participants were women and 49.6% were men. The median age was 70.0 years (range: 65-85 years), and 83.2% of the participants were in the age category of 65 to 75 years. The median BMI was 23.8 kg/m^2 (range: 16.2-31.7 kg/m^2). Demographics and baseline characteristics were generally balanced among the vaccine groups. However, in group 1, there were 44% females and 56% males.

Post-dose 1, the intake of concomitant medication of special interest was lower in group 1 (8%) (i.e. vaccinations with 5.10^{10} vp) compared to group 2 (18.4%) (i.e. vaccinations with 1.10^{11} vp; difference mainly driven by the intake of paracetamol. In group 3 (placebo), the intake was of only 3.8%.

Post-dose 2, the intake of concomitant medication of special interest was also lower in group 1 (2.1%) (i.e. vaccinations with 5.10^{10} vp) compared to group 2 (4.4%) (i.e. vaccinations with 1.10^{11} vp).

The intake of concomitant medication was highest post-dose 1 compared to post-dose 2 for the 2 tested doses.

The small number of SARS-CoV-2 seropositive participants at baseline (0 participants in group 1, and 1 participant each in groups 2 and 3) precluded any meaningful conclusion to be drawn for this subgroup.

5.4.2.2.2. Solicited AEs

In group 1, the frequency of solicited AEs was similar after the 1st (44%) and the 2nd dose (39.6%) of

$5x10^{10}$ vp Ad26.COV2.S (2 months apart). The frequencies of solicited local and systemic AEs were slightly higher or similar after the 1st dose (36% and 26%, respectively) and the 2nd (28.9% and 27.1%, respectively). There was only 1 ≥ grade 3 solicited (systemic) AE post-dose.

In group 2, the frequency of solicited AEs was higher after the 1st (71.4%) compared to the 2nd dose (57.8%) of $1x10^{11}$ vp Ad26.COV2.S (2 months apart). The frequencies of solicited local and systemic AEs were slightly higher or higher after the 1st dose (51% and 49%, respectively) compared to the 2nd (44.4% and 28.9%, respectively). There was only 1 ≥ grade 3 solicited (systemic) AE post-dose 1.

In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In groups 1 and 2, the most frequently reported solicited local AE was vaccination site pain, with a frequency similar or slightly higher post-dose 1 (36% and 46.9%, respectively) and post-dose 2 (33.3% and 40%, respectively) (mainly grade 1).

Solicited systemic AEs

In group 1, most of the solicited systemic AEs were reported with highest frequency post-dose 1 compared to post-dose 2: fatigue (22% vs. 10.4%, respectively), headache (16% vs. 4.2%, respectively), nausea (8% vs. 0%) and pyrexia (4% vs. 0%). Only myalgia was reported with lowest frequency post-dose 1 (14%) compared to post-dose 2 (22.9%).

In group 2, all solicited systemic AEs were reported with highest frequency post-dose 1 compared to post-dose 2: fatigue (34.7% vs. 17.8%, respectively), headache (24.5% vs. 8.9%, respectively), myalgia (26.5% vs. 15.6%), nausea (6.1% vs. 2.2%) and pyrexia (10.2% vs. 0%).

5.4.2.2.3. Unsolicited AEs

In group 1, the frequencies of unsolicited AEs (all) and unsolicited AEs considered related to the vaccine were higher after the 1st (30% and 12%, respectively) compared to the 2nd dose (12.5% and 4.2%, respectively) of $5x10^{10}$ vp Ad26.COV2.S (2 months apart) (mainly grade 1 and 2). There was only 1 ≥ grade 3 unsolicited AE post-dose 2 (intervertebral disc protrusion considered not related to the vaccine). There were no SAE or fatal AE.

In group 2, the frequencies of unsolicited AEs (all) and unsolicited AEs considered related to the vaccine were higher after the 1st (24.5% and 6.1%, respectively) compared to the 2nd dose (11.1% and 0%, respectively) of $1x10^{11}$ vp Ad26.COV2.S (2 months apart) (mainly grade 1 and 2). There was only 1 ≥ grade 3 unsolicited AE post-dose 1 (considered not related to the vaccine). There were no fatal AE, but 1 SAE post-dose 1 considered not related to vaccine (grade 4 intervertebral disc protrusion).

In group 1, the most frequently reported unsolicited AEs were: administration site pruritus (6%), osteoarthritis (4%), urticaria (4%) for post-dose 1; and administration site pruritus (4.2%) for post-dose 2. The reported unsolicited AEs assessed as related to vaccine were: administration site pruritus for post-dose 1 and 2 (6% and 4.2%, respectively).

In group 2, the most frequently reported unsolicited AEs were: rhinorrhoea (6.1%) for post-dose 1 (all events were reported only once post-dose 2). The reported unsolicited AEs assessed as related to vaccine were: musculoskeletal stiffness for post-dose 1 (4.1%).

After the data cut-off date of the interim CSR (22 February 2021) through the data cut-off of the interim safety update report (02 August 2021), for both groups, no new unsolicited AEs were reported. However:

- An AE leading to death was reported in 1 participant in group 2: a 70-79 year old with medical history of bilateral cataracts, stomatitis, dyslipidemia, insomnia, hypertension, and constipation at study entry received the active vaccine in the 1×10^{11}, 1×10^{11} vp group. Grade 4 acute myocardial infarction with fatal outcome was reported in the participant on Day 179. The event was considered not related to the study vaccine by the investigator.
- SAEs were reported in 3 participants in the 5×10^{10}, 5×10^{10} vp group (schwannoma, atrial fibrillation, embolic stroke, and cataract ; atrial fibrillation and embolic stroke were reported in the same participant), 2 participants in the 1×10^{11}, 1×10^{11} vp group (renal cancer and acute myocardial), and 1 participant in the placebo, placebo group (cystocele and uterine prolapse). None of the SAEs were considered related to the study vaccine by the investigator.

5.4.2.2.4. Clinical laboratory evaluation

No laboratory abnormalities were reported as AEs.

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, placebo group. Overall, the percentages of participants with abnormal safety laboratory values (biochemistry, haematology, coagulation, and urinalysis) were very low and no notable differences were noted between vaccine and placebo groups and vaccine dose levels.

5.4.2.3. AEs leading to discontinuation

In cohort 1, there were no AE leading to permanent stop of vaccination.

Three solicited AEs resulted in study vaccine discontinuation during post-dose 1 in group 2 (1×10^{11}, 1×10^{11} vp group), which were all fever/pyrexia, and no solicited AE resulted in study vaccine discontinuation during post-dose 2.

No unsolicited AE resulted in study vaccine discontinuation during post-dose 1 and post-dose 2, and 1 AE resulted in study vaccine discontinuation during the post-dose 1 follow-up phase in group 2 (blood pressure increased not related to the study vaccine on D98).

In cohort 2, there were no AE leading to permanent stop of vaccination. No unsolicited AE resulted in study vaccine discontinuation during post-dose 1 and post-dose 2 in groups 1 and 2.

One participant in the placebo, placebo group reported AEs of blood pressure increased (Grade 3; not resolved) and dizziness postural (Grade 1; resolved) during post-dose 1 follow-up (after the 28-day postvaccination), which resulted in study vaccine discontinuation. Both events were considered not related to the study vaccine by the investigator.

In cohorts 1 and 2, no new AEs leading to study vaccine discontinuation were reported after the data

cut-off date of the interim CSR (28 December 2020 or 22 February 2021, respectively) through the data cut-off of the interim safety update report (02 August 2021).

5.4.2.4. AESIs

No AESIs were reported for Cohort 1 up to the cut-off date of 28 December 2020, and for Cohort 2 up to the cut-off date of 22 February 2021.

For both groups in cohort 1, no suspected AESIs were reported after the data cut-off date of the interim CSR (28 December 2020) through the data cut-off of the interim safety update report (02 August 2021).

In cohort 2 however, after the data cut-off date of the interim CSR (22 February 2021) through the data cut-off of the interim safety update report (02 August 2021), AESIs were reported in 1 participant in the 5×10^{10}, 5×10^{10} vp group and 2 participants in the 1×10^{11}, 1×10^{11} vp group:

- On Day 161, a Grade 4 AE of embolic stroke was reported during the post-dose 2 follow-up phase in the 5×10^{10}, 5×10^{10} vp group. The platelet count results of the participant are 26.3×10^4/µL before vaccination, 26.5×10^4/µL on the day of the first vaccination, 23.5×10^4/µL on the day of the second vaccination, and 24.5×10^4/µL on the day of the event onset. The event was not a TTS. The event resolved 8 days after onset. The event was considered not related to the study vaccine by the investigator.
- On Day 57, a Grade 2 AE of thrombocytopenia was reported during the post-dose 1 follow-up phase in the 1×10^{11}, 1×10^{11} vp group. The platelet count results of the participant are 13.7×10^4/µL before vaccination, 14.7×10^4/µL on the day of the first vaccination, 10.2×10^4/µL on the day of the event onset. The event was not considered a TTS. The event resolved 175 days after onset. The event was considered not related to the study vaccine by the investigator.
- A 70-79 year-old participant: On Day 179, a Grade 4 AE of acute myocardial infarction was reported during the post-dose 2 follow-up phase in the 1×10^{11}, 1×10^{11} vp group (123 days after the booster dose (second dose)). The platelet count results of the participant are 16.4×10^4/µL before vaccination, 15.2×10^4/µL on the day of the first vaccination, 14.2×10^4/µL on the day of the second vaccination, and 11.9×10^4/µL on the day of the event onset. AntiPF4 testing was performed during the study at sample collection timepoints pre and post vaccination, results are considered negative (0.126 (study day 1), 0.127 (study day 15), 0.136 (study day 29), 0.16 (study day 57), 0.121 (study day 71), 0.139 (study day 80)). Anti PF4 testing was not performed at the time of the event. The event was assessed as a TTS, Brighton Collaboration level 3 (Brighton Collaboration 2021), Centers for Disease Control and Prevention (CDC) criteria "none Tier-1" (Shimabukuro 2021). This event resulted in death. The event was considered not related to the study vaccine by the investigator (in particular because of the too long time-to-onset).

5.5. Study COV2001

5.5.1. Methods

This is an is an ongoing randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adults aged 18 to 55 years inclusive, adults in good or stable health aged 65 years and older, and in adolescents aged 12 to 17 years inclusive. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S are being evaluated at several dose levels, as a 2-dose or a single-dose schedule.

Topline (TLR) results have been submitted (data cutoff: 11 May 2021). Adolescents are out of scope of this assessment and will not be discussed in this report.

After the 1st dose, the median follow-up is 232 days for all groups. After the 2nd dose at D57 (groups 1, 7, 2, 3, 6 and 8), the median follow-up is 174 days. After the 2nd dose at D84 (groups 9 and 10), the median follow-up is 144 days. After the 2nd dose 6 months after dose 1 (groups 4 and 5), the median follow-up is 61 days.

5.5.2. Results

Group	N (Planned)	N (Actual – 1 Dose)[a]	N (Actual – 2 Active Doses)[b]	Primary Regimen				Injection 3	Booster Vaccination					
				Day 1 (Vac 1)	Day 29 (Vac 2)	Day 57 (Vac 2)	Day 85 (Vac 2)	4 Months post-dose 2	6 months post-dose 1	8 months post-dose 1	12 months post-dose 1	14 months post-dose 1	24 months post-dose 1	26 months post-dose 1
Study COV2001 (Adult Cohorts [≥18 to ≤55 years and ≥65 years])														
Group 1[f]	75	141	137	5×10^{10} vp	-	5×10^{10} vp	-	1.25×10^{10} vp						
Group 7[f,j]	50			5×10^{10} vp	5×10^{10} vp	-	-	1.25×10^{10} vp						
Group 2[g]	75	81	73	2.5×10^{10} vp	-	2.5×10^{10} vp	-	1.25×10^{10} vp						
Group 3[g]	75	75	74	1.25×10^{10} vp	-	1.25×10^{10} vp	-	1.25×10^{10} vp						
Group 4[g]	75	74	68	1×10^{11} vp	-	Placebo	-	1.25×10^{10} vp						
Group 5[f]	75	81	74	5×10^{10} vp	-	Placebo	-	1.25×10^{10} vp						
Group 9[f]	50	53	51	5×10^{10} vp	-	-	5×10^{10} vp	1.25×10^{10} vp						
Group 6[d]	25	52	-	Placebo	-	Placebo	-	Placebo						
Group 8[d,j]	25			Placebo	Placebo	-	-	Placebo						
Group 10[d]	25	25	-	Placebo	-	-	Placebo	Placebo						

Groups 7 and 8 had a 1-month interval planned per protocol; however, due to a study pause participants received their booster dose (second dose) at 2 months.

The following groups are of main interest:

- groups 1+7 data: D1 and D57 vaccinations with 5.10^{10} vp (N=141 1st dose, N=137 2nd dose)
- group 9 data: D1 and D85 vaccinations with 5.10^{10} vp (N=53 1st dose, N=51 2nd dose)

The following data are supportive:

- group 2: D1 and D57 vaccinations with $2.5.10^{10}$ vp (N=81 1st dose, N=73 2nd dose)
- group 3: D1 and D57 vaccinations with $1.25.10^{10}$ vp (N=75 1st dose, N=74 2nd dose)
- group 5: D1 vaccination with 5.10^{10} vp (N=81); D57 placebo (N=77); 4 months post-dose 2 with $1.25.10^{10}$ vp (i.e. 6 months post-dose 1) (N=74)
- group 4: D1 vaccination with 1.10^{11} vp (N=74); D57 placebo (N=72); 4 months post-dose 2 with $1.25.10^{10}$ vp (i.e. 6 months post-dose 1) (N=68).

The last groups are of less interest for the purpose of this variation. The 3rd dose data ($1.25.10^{10}$ vp) 4 months post-dose 2 will not be assessed in this report.

5.5.2.1. Demographic and baseline characteristics

Most participants were white (96.9%). Overall, 36.8% of participants were female and 63.2% were male. The median age was 49.0 years (range: 18-84 years); 35.6% of participants were between 18 and 40 years old, 28.5% were between 41 and 55 years old, 31.3% were between 65 and 75 years old, and 4.6% were older than 75. The median body mass index (BMI) was 24.7 kg/m^2 (range: 16.8-30.0 kg/m^2). Demographics, other than gender, and baseline characteristics in adults were generally well balanced between the different groups. However, in group 10 (placebo), there were 52% females

and 48% males. The distribution of participants across sites was well balanced between the different groups.

Post-dose 1, the intake of concomitant medication of special interest was lower in group 3 (8%) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) vs. group 2 (16%) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) vs. groups 1+7 (27%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart), group 9 (28.3%) (i.e. vaccinations with 5.10^{10} vp – 3 months apart), group 5 (24.7%) (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart) and group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart); difference mainly driven by the intake of paracetamol. In the placebo groups, the intake was 3.8% in groups 6 + 8 (placebo – 2 months apart) and 12% in group 10 (placebo – 3 months apart).

Post-dose 2, the intake of concomitant medication of special interest was lower in group 3 (6.8%) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) vs. group 2 (17.8%) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) vs. groups 1+7 (24.8%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart) and group 9 (23.5%) (i.e. vaccinations with 5.10^{10} vp – 3 months apart); difference mainly driven by the intake of paracetamol. In the placebo groups, the intake was 6.1% in groups 6 + 8 (placebo – 2 months apart) and 12% in group 10 (placebo – 3 months apart).

Overall, the intake of concomitant medication was similar post-dose 1 compared to post-dose 2 for the 3 tested doses (2 or 3 months apart).

However, in group 5 (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart) and in group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart), the intake of concomitant medication of special interest was higher post-dose 1 (24.7% and 44.6%, respectively) compared to post-antigen presentation at 6 months (14.9% and 10.3%).

The number of SARS-CoV-2 seropositive participants at baseline per group was not provided. However, it is doubtful that the number would be high enough to have meaningful conclusions.

5.5.2.2. Solicited AEs

In groups 1+7 (i.e. vaccinations with 5.10^{10} vp – 2 months apart) and group 9 (i.e. vaccinations with 5.10^{10} vp – 3 months apart), the frequency of solicited AEs was similar after the 1st (66% and 62.3%, respectively) and the 2nd dose (69.3% and 62.7%, respectively). The frequencies of solicited local AEs were slightly higher or similar after the 1st dose (53.2% and 39.6%, respectively) and the 2nd (46% and 39.2%, respectively). The frequencies of solicited systemic AEs were similar or higher after the 1st dose (59.6% and 60.4%, respectively) and the 2nd (59.1% and 51%, respectively). The frequencies of ≥ grade 3 solicited AEs (mainly systemic) were higher or similar after the 1st dose (3.5% and 5.7%, respectively) and the 2nd (2.2% and 3.9%, respectively).

In group 5 (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart) and group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart), the frequency of solicited AEs was higher after the 1st (67.9% and 77%, respectively) compared to the post-antigen presentation (54.1% and 54.4%). The frequency of solicited local AEs was slightly higher or similar after the 1st dose (51.9% and 52.7%) and the post-antigen presentation (47.3% and 45.6%). The frequencies of solicited systemic AEs were higher after the 1st dose (61.7% and 75.7%) compared to the post-antigen presentation (37.8% and 33.8%).

Overall, a trend towards an increase in the frequency solicited AEs (local and systemic) was observed with increasing vaccine doses:

- Post-dose 1, frequency of all solicited AEs, solicited local AEs, and solicited systemic AEs, was lower or similar in group 3 (53.3%, 32%, and 41.3%, respectively) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) vs. group 2 (53.1%, 33.3% and 43.2%, respectively) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) vs. groups 1+7 (66%, 53.2% and 59.6%, respectively) (i.e. vaccinations with 5.10^{10} vp – 2 months apart).
- Post-dose 2, frequency of all solicited AEs, solicited local AEs, and solicited systemic AEs, was lower or similar in group 3 (52.7%, 39.2%, and 33.8%, respectively) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) vs. group 2 (61.6%, 45.2% and 43.8%, respectively) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) vs. groups 1+7 (69.3%, 46% and 59.1%, respectively) (i.e. vaccinations with 5.10^{10} vp – 2 months apart).

In all groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

In groups 1+7 (i.e. vaccinations with 5.10^{10} vp – 2 months apart) and group 9 (i.e. vaccinations with 5.10^{10} vp – 3 months apart), the frequency of the most frequently reported solicited local AE (vaccination site pain) was higher or similar after the 1st dose (53.2% and 39.6%, respectively) and the 2nd (46% and 39.2%, respectively).

In group 5 (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart) and in group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart), the frequency of the most frequently reported solicited local AE (vaccination site pain) was similar after the 1st dose (51.9% and 52.7%, respectively) and the post-antigen presentation (47.3% and 45.6%).

Overall, a trend towards an increase in the frequency of the most frequently reported solicited local AE was observed with increasing vaccine doses:

- Post-dose 1, frequency of vaccination site pain was lower or similar in group 3 (32%) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) vs. group 2 (33.3%) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) vs. groups 1+7 (53.2%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart).
- Post-dose 2, frequency of vaccination site pain was lower in group 3 (39.2%) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) vs. group 2 (43.8%) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) vs. groups 1+7 (46%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart).

Solicited systemic AEs

In groups 1+7 (i.e. vaccinations with 5.10^{10} vp – 2 months apart), all solicited systemic AEs were reported with highest or similar frequency post-dose 1 compared to post-dose 2: fatigue (45.4% vs. 45.3%, respectively), headache (41.1% vs. 36.5%), myalgia (34% vs. 27%), nausea (9.2% vs. 7.3%) and pyrexia (9.9% vs. 3.6%).

Overall, a trend towards an increase in the frequency of the all reported solicited systemic AEs was observed with increasing vaccine doses:

- Post-dose 1, in group 3 (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart), group 2 (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) and groups 1+7 (53.2%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart), the frequencies were: fatigue (28% vs. 28.4% vs. 45.4%,

respectively), headache (25.3% vs. 27.2% vs. 41.1%), myalgia (9.3% vs. 11.1% vs. 34%), nausea (4% vs. 4.9% vs. 9.2%) and pyrexia (0% vs. 6.2% vs. 9.9%).

- Post-dose 2, in group 3 (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart), group 2 (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) and groups 1+7 (53.2%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart), the frequencies were: fatigue (21.6% vs. 20.5% vs. 45.3%, respectively), headache (20.3% vs. 32.9% vs. 36.5%), myalgia (6.8% vs. 15.1% vs. 27%), nausea (2.7% vs. 9.6% vs. 7.3%) and pyrexia (0% vs. 0% vs. 3.6%).

In group 9 (i.e. vaccinations with 5.10^{10} vp – 3 months apart), all solicited systemic AEs were reported with highest or similar frequency post-dose 1 compared to post-dose 2: fatigue (45.3% vs. 45.1%, respectively), headache (39.6% vs. 27.5%), myalgia (35.8% vs. 21.6%), nausea (9.4% vs. 5.9%) and pyrexia (7.5% vs. 5.9%).

In group 5 (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart), all solicited systemic AEs were reported with highest frequency post-dose 1 compared to the post-antigen presentation: fatigue (45.7% vs. 28.4%, respectively), headache (40.7% vs. 24.3%), myalgia (38.3% vs. 14.9%), nausea (11.1% vs. 9.5%) and pyrexia (17.3% vs. 0%).

In group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart), all solicited systemic AEs were reported with highest frequency post-dose 1 compared to the post-antigen presentation: fatigue (51.4% vs. 22.1%, respectively), headache (60.8% vs. 17.6%), myalgia (37.8% vs. 13.2%), nausea (20.3% vs. 4.4%) and pyrexia (20.3% vs. 0%).

Solicited AEs by age categories

When comparing the number of participants with solicited AEs post-dose 1 by age category, a trend towards a decrease in the frequency and severity of solicited local AEs with increasing age of participants was observed in all active vaccine groups Ad26.COV2.S administration ($1.25.10^{10}$ vp, $2.5.10^{10}$ vp, 5.10^{10} vp or 1.10^{11} vp Ad26.COV2.S).

Moreover, for all age categories, a trend toward an increase in the frequencies of solicited local and systemic AEs were observed with increasing dose of vaccine.

5.5.2.3. Unsolicited AEs

In groups 1+7 (i.e. vaccinations with 5.10^{10} vp – 2 months apart) and group 9 (i.e. vaccinations with 5.10^{10} vp – 3 months apart), the frequency of unsolicited AEs was overall similar after the 1st (28.4% and 15.1%, respectively) compared to the 2nd dose (24.8% and 19.6%, respectively) (mainly grade 1 or 2). The frequencies of unsolicited AEs considered related to the vaccine were overall similar after the 1st dose (5.7% and 1.9%, respectively) and the 2nd (8% and 2%, respectively). The frequencies of ≥ grade 3 unsolicited AEs were higher after the 1st dose (2.1% and 1.9%, respectively) and the 2nd (0% and 0%, respectively).

In groups 1+7 (i.e. vaccinations with 5.10^{10} vp – 2 months apart) and group 9 (i.e. vaccinations with 5.10^{10} vp – 3 months apart), the frequency of unsolicited AEs was overall higher or similar during the post-dose 1 follow-up (7.1% and 17%, respectively) and during the post-dose 2 follow-up (7.4% and 3.9%, respectively) (mainly grade 1 or 2). The frequencies of unsolicited AEs considered related to the vaccine were overall similar during the post-dose 1 follow-up (2.1% and 0%, respectively) and during the post-dose 2 follow-up (0.7% and 0%, respectively).

There were no fatal AE, but, post-dose 2 follow-up, there were 1 SAE in groups 1+7 (i.e. vaccinations with 5.10^{10} vp – 2 months apart) and 1 SAE in group 9 (i.e. vaccinations with 5.10^{10} vp – 3 months apart) (none considered related to vaccine).

In group 5 (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart), the frequencies of unsolicited AEs and unsolicited AEs considered related to the vaccine were higher after the 1st (37% and 8.6%, respectively) compared to the post-antigen presentation (14.9% and 5.4%) (no ≥ grade 3 unsolicited AEs).

In group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart), the frequencies of unsolicited AEs and unsolicited AEs considered related to the vaccine were higher after the 1st (44.6% and 13.5%, respectively) compared to the post-antigen presentation (7.4% and 4.4%) (no ≥ grade 3 unsolicited AEs).

The only fatal AE was reported in group 2 (D1 and D57 vaccinations with $2.5.10^{10}$ vp) (unknown cause considered as unrelated to study vaccine).

Post-dose 1, frequency of unsolicited AEs was lower in group 3 (18.7%) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) compared to group 2 (32.1%) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) which was similar to groups 1+7 (28.4%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart). Post-dose 2, frequency of unsolicited AEs was similar in group 3 (20.3%) (i.e. vaccinations with $1.25.10^{10}$ vp – 2 months apart) compared to group 2 (24.7%) (i.e. vaccinations with $2.5.10^{10}$ vp – 2 months apart) and groups 1+7 (24.8%) (i.e. vaccinations with 5.10^{10} vp – 2 months apart).

Only headache was reported with a frequency of at least 10% in any group (11.1% in group 2, post-dose 1 after $2.5x10^{10}$ vp Ad26.COV2.S). Post-dose 1, headache was reported with a frequency of 4% in group 3 ($1.25x10^{10}$ vp), 5% in groups 1+7 ($5x10^{10}$ vp), 12.3% in group 5 ($5x10^{10}$ vp) and 6.8% in group 4 ($1x10^{11}$ vp). Headache was also reported post-dose 2 in group 9 ($5x10^{10}$ vp, $5x10^{10}$ vp 3 months apart) with a frequency of 3.9%.

Post-dose 1, there was no unsolicited AE related to vaccination in group 3 ($1.25x10^{10}$ vp), 11.1% unsolicited AE related to vaccination in group 2 ($2.5x10^{10}$ vp; chills being the more frequent), 5.7% unsolicited AE related to vaccination in groups 1+7 ($5x10^{10}$ vp; chills being the more frequent), 1.9% unsolicited AE related to vaccination in group 9 ($5x10^{10}$ vp; only fatigue), 8.6% unsolicited AE related to vaccination in group 5 ($5x10^{10}$ vp; chills being the more frequent), and), and 13.5% unsolicited AE related to vaccination in group 4 ($1x10^{11}$ vp; chills being the more frequent).

Post-dose 2, there were 5.4% unsolicited AE related to vaccination in group 3 ($1.25x10^{10}$ vp, $1.25x10^{10}$ vp 2 months apart; all AEs reported only once), 5.5% unsolicited AE related to vaccination in group 2 ($2.5x10^{10}$ vp, $2.5x10^{10}$ vp 2 months apart; all AEs reported only once), 8% unsolicited AE related to vaccination in groups 1+7 ($5x10^{10}$ vp, $5x10^{10}$ vp 2 months apart; only fatigue being twice), and 2% unsolicited AE related to vaccination in group 9 ($5x10^{10}$ vp, $5x10^{10}$ vp 3 months apart; only oral herpes).

Post-antigen presentation, there were 5.4% unsolicited AE related to vaccination in group 5 (i.e. vaccinations with 5.10^{10} vp and $1.25.10^{10}$ vp – 6 months apart); chills being the more frequent (2.5%).

Post-antigen presentation, there were 4.4% unsolicited AE related to vaccination in group 4 (i.e. vaccinations with 1.10^{11} vp and $1.25.10^{10}$ vp – 6 months apart); injection site pain, headache, lymphadenopathy and nausea being the more frequent (1.5% each).

5.5.2.4. Clinical laboratory evaluation

Not provided

5.5.2.5. AEs leading to discontinuation

Upon request more details about AE leading to discontinuation have been provided: no participants discontinued the study due to an AE. Three participants discontinued the vaccine treatment due to an AE:

- One participant in the Ad26.COV2.S $5x10^{10}$ vp, placebo group due to a grade 4 lung adenocarcinoma (SAE) deemed not related to the vaccine 15 days after the placebo dose.
- A second participant in the Ad26.COV2.S $5x10^{10}$ vp, Ad26.COV2.S $5x10^{10}$ vp group had a grade 3 acute myeloid leukaemia (SAE) deemed not related to the vaccine 63 days after the booster dose (second dose).
- A third participant in the Ad26.COV2.S $2.5x10^{10}$ vp group experienced a grade 1 paraesthesia (transient paresthesias in both hands and face) deemed related to the vaccine 37 days after the first dose.

5.5.2.6. AESIs

Two thrombotic events have been reported. One participant in the 5×10^{10} vp, PL (56-day) group had Grade 2 thrombophlebitis at Day 2 (ie, one day after the first vaccination) and 1 participant in the 5×10^{10}, 5×10^{10} vp (56-day) group had Grade 3 ischemic stroke 8 days post antigen presentation (after a 3rd dose $1.25.10^{10}$ vp 4 months post-dose 2) (no platelet count data available).

5.6. Study COV2008

5.6.1. Methods

The study COV2008 is an ongoing, randomized, double-blind, Phase 2 study to evaluate the immunogenicity, reactogenicity and safety of Ad26.COV2.S (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) administered as booster vaccination in adults 18 years of age or older at least 6 months after receiving a primary vaccination with Ad26.COV2.S (1-dose in study COV3001, N=770) or Pfizer's BNT162b2 (2-dose, N=770).

The study included the following cohorts:

- Cohort 1: 370 participants (including 7-day reactogenicity data from 244 participants), who have received an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) at least 6 months after primary single-dose Ad26.COV2.S (5×10^{10} vp) vaccination.
- Cohort 2: Dose level-blinded reactogenicity data are also available from 161 participants (including 7-day reactogenicity data from 76 participants) who have received an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) $\geqslant$6 months after primary (2-dose) administration of Pfizer's BNT162b2.

Data entry and collection were still ongoing at the time of the data extraction for this study (7 September 2021). Not all participants had completed the 28-day post-vaccination reporting period at

the time of the data extraction. Therefore, these outputs represent an incomplete snapshot. Standard data cleaning and reconciliation activities had also not been performed on these data, implying that data are subject to change in further analyses.

The median duration of the follow-up is unknown at this stage.

Dose level-blinded reactogenicity have been provided after the booster vaccination for both cohorts.

5.6.2. Results

5.6.2.1. Cohort 1

5.6.2.1.1. Demographic and baseline characteristics

There were 370 participants (aged ≥18 years) who received primary vaccination with Ad26.COV2.S followed by an Ad26.COV2.S booster (5×10^{10} or 2.5×10^{10} or 1×10^{10} vp) ≥6 months later, 244 for whom 7-day reactogenicity data are available. Of these 244 participants, 123 (50.4%) were female, 121 (49.6%) were male, and 220 (90.2%) were white. The median age was 57.0 years (range: 22.0-87.0) and the median BMI was 27.2 kg/m² (range: 17.6-58.3).

5.6.2.1.2. Solicited AEs

For these 244 participants, 63.5% reported solicited AEs post-dose 1: 51.2% reported solicited local AEs (mainly driven by vaccination site pain) and 47.1% reported solicited systemic AEs (the majority being considered as related to study vaccine). Almost all solicited AEs were Grade 1 or 2 in severity, and one Grade 3 solicited local AE was reported (vaccination site erythema). The most frequently reported solicited systemic AEs were fatigue (36.1%), headache (26.2%), and myalgia (25.4%). There were also 7.8% nausea and 0.8% pyrexia.

5.6.2.1.3. Unsolicited AEs

For the 370 participants, almost all unsolicited AEs reported were Grade 1 in severity, none were Grade 3 or 4. The most frequently reported unsolicited AE was fatigue (mainly assessed as related to study vaccine). No SAEs were reported.

5.6.2.2. Cohort 2

5.6.2.2.1. Demographic and baseline characteristics

There were 161 participants (aged ≥18 years) who received an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) at least 6 months after primary (2-dose) administration of Pfizer's BNT162b2, 76 for whom 7-day reactogenicity data are available. Of these 76 participants, 43 (56.6%) were female, 33 (43.4%) were male, and 70 (92.1%) were white. The median age was 46 years (range: 20-79) and the median BMI was 26.8 kg/m² (range: 19.3-39).

5.6.2.2.2. Solicited AEs

For these 76 participants, 81.6% reported solicited AEs post-dose 1: 69.7% reported solicited local AEs (mainly driven by vaccination site pain) and 71.1% reported solicited systemic AEs (all considered as related to study vaccine). Almost all solicited AEs were Grade 1 or 2 in severity, and one Grade 3 solicited systemic AE was reported (pyrexia). The most frequently reported solicited systemic AEs were fatigue (56.6%), headache (51.3%), and myalgia (48.7%). There were also 19.7% nausea and 3.9% pyrexia.

5.6.2.2.3. Unsolicited AEs

For the 161 participants, almost all unsolicited AEs reported were Grade 1 in severity, none were Grade 3 or 4. The most frequently reported unsolicited AEs were arthralgia, headache, fatigue, chills and myalgia (around half of them were assessed as related to study drug). No SAEs were reported.

5.7. Study COV3001

5.7.1. Methods

VAC31518COV3001 is ongoing multicenter, randomized, 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. The planned total sample size was up to approximately 40,000 participants.

Participants were randomized in parallel in a 1:1 ratio to receive 1 dose of Ad26.COV2.S or placebo at Day 1 as shown in Table below. The study vaccines were administered by intramuscular injection in the deltoid muscle. Ad26.COV2.S was administered at a dose level of 5×10^{10} vp.

Table 17: Vaccination Schedule VAC31518COV3001

Group	N (Planned)	Day 1	Unblinding Visit/Month 6*
1	20,000	Ad26.COV2.S (5×10^{10} vp)	-
2	20,000	Placebo	Ad26.COV2.S (5×10^{10} vp)

EUA = Emergency Use Authorization; IEC = Independent Ethics Committee; IRB = Institutional Review Board; N = number of participants; vp = virus particles.

Note: It was intended that a minimum of approximately 30% of recruited participants were ≥60 years of age and approximately 20% of recruited participants were ≥18 to <40 years of age.

* All participants were unblinded (informed whether they received placebo or Ad26.COV2.S) at the on-site unblinding visit following EUA, conditional licensure, or approval in any country or at the Month 6 visit at the latest. After approval of protocol Amendment 4 by the local Health Authority and IEC/IRB, the study continued as an open-label study. Participants who received placebo on Day 1 were offered to receive a single dose of Ad26.COV2.S 5×10^{10} vp under conditions delineated in the protocol.

The study consists of a screening phase of up to 28 days, a 52-week study period, and a long-term follow-up period of 1 additional year. The end-of-study is considered as the completion of the last visit for the last participant in the study.

A total of 43,788 participants were vaccinated (21,898 in the Ad26.COV2.S group and 21,890 in the placebo-group - FAS). The median follow-up in the FAS was 123.0 days (double-blind). At the time of the final analysis of the double-blind phase, 11,290 (25.8%) participants in the FAS had at least 6 months (defined as 24 weeks) of double-blind follow-up.

This final analysis of the double-blind phase of the study includes data from the Safety Subset (ie, a subset of the FAS) for the analysis of solicited and unsolicited AEs (3,356 participants in the Ad26.COV2.S 5×10^{10} group and 3380 in the placebo-group) and data from the FAS for the analysis of MAAEs, deaths, other SAEs and AEs leading to study/vaccine discontinuation.

Final analysis topline (TLR) results have been submitted (data cutoff: 9 July 2021).

5.7.2. Results

5.7.2.1. Demographic and baseline characteristics

No relevant differences in demographics and baseline characteristics were observed between the Ad26.COV2.S group and the placebo-group.

Overall in the FAS, 58.7% of participants were white and 19.4% were black or African American. Subjects were coming from Latin America (40.9%), Northern America (44.1%), and Southern Africa (15%) (none from Europe). 54.9% of participants were male. The median age was 52 years (range: 18; 100 years) and 33.5% of participants were ≥60 years of age. The median BMI was 27.91 kg/m^2 (range: 11.9-82.6 kg/m^2). 42% of subjects had at least 1 comorbidity at baseline; The main comorbidity being obesity (28.7% of subjects). There were 2,253 participants with positive SARS-CoV-2-serostatus and/or PCR status at baseline in the 5.10^{10} vp group and 2,208 in the placebo group.

In the safety subset, there were 166 participants with positive SARS-CoV-2-serostatus and/or PCR status at baseline in the 5.10^{10} vp group and 162 in the placebo group.The demographic characteristics have not been provided for the safety subset.

The intake of concomitant medication has not been provided for the FAS and the safety subset.

5.7.2.2. Solicited AEs

As expected, the frequencies for local and systemic solicited AEs were higher in the Ad26.COV2.S group (54.8% and 60.2%, respectively) compared to the placebo-group (20.2% and 38.7%). In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

In the Ad26.COV2.S group, a general trend for lower reactogenicity (solicited local and systemic AEs) was observed in adults ≥60 years compared to younger adults (18-59 years). This trend was not observed in the placebo group. Overall, the reactogenicity was similar in participants with positive or negative SARS-CoV-2-serostatus and/or PCR status at baseline in both groups.

Solicited local AEs

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 (53.1%) compared to participants in the placebo group (17.6%) (mainly grade 1 and 2). All solicited local AEs were transient in nature and reported as resolved. Grade 3 local solicited AEs were reported in 0.6% of participants in the Ad26.COV2.S group (no grade 4).

Solicited systemic AEs

In the Ad26.COV2.S group, the most frequently reported solicited systemic AEs were headache (43.3%), fatigue (42.3%), and myalgia (37.1%) (mainly grade 1 and 2) (nausea 16.4% and pyrexia 7.4%). Most solicited systemic AEs were transient in nature and reported as resolved. Grade 3 solicited systemic AEs were reported in 2.3% of the subjects. There was one event of myalgia grade 4.

Overall, the reactogenicity profile is similar to the initial assessment for conditional MA.

5.7.2.3. Unsolicited AEs

Overall, unsolicited AEs were reported with similar frequencies in both groups: 13.6% of participants in the Ad26.COV2.S group and 12.5% of participants in the placebo group. Most unsolicited AEs were Grade 1 or Grade 2 in severity; Unsolicited AEs of at least Grade 3 were reported in 27 (0.8%) participants in the Ad26.COV2.S group compared with 23 (0.7%) in the placebo-group. Unsolicited AEs considered related to study vaccine by investigator were slightly more reported in the Ad26.COV2.S group (6.8%) compared to the placebo group (4.1%). The frequencies of SAEs (safety subset, post dose) were similar in both groups: 0.4% in Ad26.COV2.S group (13 SAEs including 2 considered as related to study vaccine by investigator) and 0.3% in placebo group (10 SAEs; none considered related). There was 1 fatal AE in the placebo group.

In the Ad26.COV2.S and the placebo groups, the most frequently reported unsolicited AEs, which were also recorded as solicited AEs, were headache (1.9% vs. 2.1%, respectively), myalgia (1.2% vs. 1.5%), and fatigue (1.4% vs. 2.1%). The most frequently reported unsolicited AEs that were not recorded as solicited AEs were chills (2.1% vs. 0.7%), arthralgia (1.1% vs 0.8%), nasal congestion (1.2% vs. 1.1%), cough (1% vs. 1%), and diarrhoea (1% vs. 1%). Imbalances with higher frequencies in the Ad26.COV2.S group versus the placebo group were observed for the following unsolicited AEs: vaccination site pain (1.1% vs. 0.5%) and muscular weakness (0.3% vs. 0.1%).

Unsolicited AEs related to vaccination by investigator assessment were reported for 6.8% and 4.1% of participants in the Ad26.COV2.S and the placebo group, respectively. In the Ad26.COV2.S group, the most frequently reported unsolicited AEs related to vaccination were chills (1.7% vs. 0.3% in the placebo group), vaccination pain (1.1% vs. 0.4%, respectively), fatigue (0.9% vs. 1.2%), and headache (0.9% vs. 0.7%).

Overall, the most frequently reported unsolicited AEs are recognised ADRs of the Janssen COVID-19 vaccine.The safety profile is similar to the initial assessment for conditional MA.

5.7.2.4. Fatal AEs and SAEs

Fatal AEs

In the FAS, 83 fatal events were reported in the double-blind phase: 28 in the Ad26.COV2.S group (0.1% of 21,898 subjects) and 55 in the placebo-group (0.3% of 21,890 subjects): 4 and 19, respectively, were reported in subjects SARS-CoV-2 positive during the study (mainly COVID-19 associated deaths); 1 and 1, respectively in subjects SARS-CoV-2 positive at baseline (COVID-19 pneumonia); and 23 and 35, respectively, in subjects without SARS-CoV-2 positive test during the study. The distribution of fatal events by SOC was balanced across groups and does not raise a concern: General disorders and administration site conditions (9 each), Cardiac disorders (5 each),

Infections and infestations (4 vs. 5, respectively), Gastrointestinal disorders (2 vs. none), Respiratory, thoracic and mediastinal disorders (2 each), Injury, poisoning and procedural complications (1 vs. 2), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (1 vs. 2) (including 2 events in same subject in Ad26.COV2.S group); all the others events were reported only in placebo group.

All fatal events reported during the double-blind phase were considered unrelated to the study vaccine (Ad26.COV2.S or placebo) by the investigator.

Of note, during the entire study (double-blinded and open-labelled study), 103 fatal AEs were reported in 100 participants, of which 40 occurred in participants who received Ad26.COV2.S (0.1% of 35,581 subjects). Four deaths were reported after vaccination with Ad26.COV2.S in the open-label phase (including 2 not related to COVID-19). One of these events was considered related to the study vaccine by the investigator. The participant was reported with grade 4 pulmonary embolism 57 days after vaccination with Ad26.COV2.S in the open-label phase. After database lock, upon review of the autopsy report, the investigator re-assessed this death to unrelated. No other death reported during the study was considered related to the study vaccine by the investigator.

Overall, in the FAS, there were no fatal events considered related to Ad26.COV2.S. during the double-blind phase and the open-labelled study, and there were less fatal AEs in Ad26.COV2.S. group compared to placebo group.

SAEs

In the FAS, a total of 235 (1.1% of 21,898 subjects) participants reported SAEs in the Ad26.COV2.S group compared with 358 (1.6% of 21,890 subjects) participants in the placebo-group, during the double-blind phase. A total of 223 (1.0%) participants reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared with 265 (1.2%) participants in the placebo-group, during the double-blind phase. 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 (0.2% [49 participants] in the Ad26.COV2.S group and 0.3% [61 participants] in the placebo group). All other SAEs were reported with frequencies by SOC ≤ 0.1% in the Ad26.COV2.S group.

During the entire study (double-blinded and open-labelled study), 436 SAEs were reported in participants who received Ad26.COV2.S (1.2% of 35,581 subjects).

Additional details have been provided about SAEs considered related to the study vaccine by investigator assessment: During the entire study, 19 participants reported a total of 21 SAEs which were considered to be related to the study vaccine by the investigator: 19 events (reported by 18 participants) after Ad26.COV2.S vaccination (3 cases of ischemic stroke, 2 cases of Bell's Palsy, 2 cases of pulmonary embolism, 2 cases of deep vein thrombosis, GBS, venous thrombosis limb, retinal vein thrombosis, atrial fibrillation, pericarditis, complex regional pain syndrome, post vaccination syndrome, hypersensitivity, headache and asthma; some of them reported after cross-over vaccination) and 2 events (reported by 1 participant) after placebo (Epstein-Barr virus infection and atrial flutter)**.**

One SAE of thromboembolic event with thrombocytopenia (venous transverse sinus thrombosis and cerebral hemorrhage) reported following administration of Ad26.COV2.S was confirmed as thrombosis with thrombocytopenia meeting both Level 1 criteria using the Brighton Collaboration level of certainty and the Centers for Disease Control and Prevention (CDC) definition for a tier 1 TTS case and could

therefore be confirmed as TTS according to both case definitions. Venous thromboembolism and TTS are recognized ADRs in the SmPC. Non-haemorrhagic stroke is an identified AESI in the RMP.

In study COV3001, 14 SAEs of supraventricular tachycardia, atrial fibrillation, or atrial flutter were reported after vaccination in 12 participants (7 in Ad26.COV2.S group and 5 in placebo group). Of these 14 SAEs, 2 (1 atrial flutter [placebo group], 1 atrial fibrillation [Ad26.COV2.S 5×10^{10} vp group]) were considered related to study vaccination by the investigator. However, for the event in the active group, based on the pre-existing risk factors and long time to onset of 181 days, the event of atrial fibrillation is assessed to have an inconsistent causal association to vaccination, per WHO causality classification for adverse events following immunization. 19 SAEs of supraventricular tachycardia, atrial fibrillation, or atrial flutter were reported after vaccination in 18 participants in other Ad26.COV2 clinical trials: in studies COV3009 (7 in Ad26.COV2.S group, 5 in placebo group and 3 after crossover), COV1001 (1 in Ad26.COV2.S 5×10^{10} vp, Ad26.COV2.S 5×10^{10} vp group), COV1002 (1 in Ad26.COV2.S 5×10^{10} vp group), and COV2008 (1 blind), none of which were considered related to study vaccination by the investigator.

The MAH also provided a cumulative review from reports of supraventricular tachycardia, atrial fibrillation, or atrial flutter received from post-marketing experience until 24th August 2021, a total of 200 case reports of arrhythmias were reported, majority from the US (n=123). Of the 200 cases, 82 concerned males, 108 females, and 10 did not report sex. The age range was 18 to 95 years. Among the Arrythmia cases, a total of 55 cases were reported as atrial fibrillation and a further 5 were reported as atrial flutter. A further 46 were reported as arrhythmia (not further specified) and 37 as heart rate irregular (not further specified). The mean and median time to onset was 11.9 days and 3 days, respectively. Observed versus Expected (O/E) analysis in the US and EU did not raise any concern.

In conclusion, cumulative analysis of clinical and post-marketing safety data of events of supraventricular tachycardia, atrial fibrillation or atrial flutter did not show an increase in risk following vaccination with Ad26.COV2.S.

5.7.2.5. Medically-attended Adverse Events

In the FAS, double blind phase, similar frequency of subjects reported at least one MAAEs of grade 3 in both groups: 1.2% in the Ad26.COV2.S group and 1.6% in the placebo group. No MAAEs grade 3 were reported with higher frequency in the Ad26.COV2.S group compared to the placebo group.

Additional details have been provided about MAAEs not associated with COVID-19. The overall frequency of MAAEs not associated with COVID-19 was similar in both groups: 7.4% versus 8.0% in the Ad26.COV2.S and placebo groups, respectively (with similar distribution by SOC).

The overall frequency of MAAEs assessed as related to the study vaccine, not associated with COVID-19, was similar in both the Ad26.COV2.S (54 MAAEs – 0.2%) and placebo group (37 MAAEs – 0.2%). In the Ad26.COV2.S group, the MAAEs were mainly in the following SOCs: general disorders and administration site conditions (13 MAAEs), musculoskeletal and connective tissue disorders (13 MAAEs), nervous system (8 MAAEs) and Skin and subcutaneous tissue disorders (7 MAAEs).

5.7.2.6. AEs leading to discontinuation

No unsolicited AEs leading to study discontinuation were reported.

5.7.2.7. AESIs

The MAH has provided more details about AESIs reported in COV3001. Only TTS was defined as an AESI for the COVID-19 vaccine program, but in addition, a number of Adverse Events of Interest (AEIs) was established, based on either a numerical imbalance and/or potential causal relationship identified: allergic reactions, tinnitus, convulsions/seizures, thrombotic and thromboembolic events, demyelinating disorders/GBS, and Bell's palsy.

In the FAS, similar frequency of subjects reported at least one treatment emergent AEI in both groups (1.7% in the Ad26.COV2.S group and 1.6% 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.

There were some numerical imbalances in the occurrence of some AEIs between the Ad26.COV2.S and placebo group: tinnitus (15 vs. 4, respectively), seizure (7 vs. 2), rash (46 vs. 35), urticaria (13 vs. 6), deep vein thrombosis (11 vs. 3), pulmonary embolism (10 vs. 5), and ischemic stroke (3 vs. none). There was no anaphylaxis reported in the active group (vs. 1 in the placebo), 1 GBS in each group, and no immune thrombocytopenia reported in the active group (vs. 1 in the placebo group.

There were 53 subjects with AEIs assessed as related to vaccination in the active group (0.2%) versus 21 in the placebo group (0.1%). The following related AEIs by investigator assessment were numerically imbalanced between the Ad26.COV2.S and placebo group: tinnitus (3 vs. none, respectively), hypersensitivity events (29 vs. 11, with in particular: rash (15 vs. 7), urticaria (4 vs. none), and eyelid oedema (2 vs. none)), thromboembolic events (4 vs. none: 2 deep vein thrombosis, 1 ischemic stroke and 1 retinal vein thrombosis in active group) and haemorrhagic disorders (9 vs. 3, mainly local injection site AEs).

Most of these events (Tinnitus, rash, hypersensitivity, urticaria, venous thromboembolism (including pulmonary embolism), Guillain-Barré syndrome, Immune thrombocytopenia, injection site erythema and swelling) are recognized ADRs in the SmPC. Non-haemorrhagic stroke and generalized convulsion are identified AESIs and are events under close monitoring.

With regards to the occurrence of seizures, the MAH has clarified that, in study COV3001, there were 21 events of seizure/convulsion reported by 20 participants. Twelve events were reported in the Ad26.COV2.S, 7 in the placebo group and 2 after a crossover vaccination. Six of these events were serious and they were all assessed as not related to vaccination: 2 in the Ad26.COV2.S, 2 in the placebo group (including 1 fatal) and 2 after a crossover vaccination (including 1 fatal). One non-serious adverse event was considered as related to study vaccination by the Investigator. The event was reported in an 18-29 year old participant that received Ad26.COV2.S and 115 days after vaccination presented an increase on the frequency of seizures of that lasted 5 days and recovered.

Six events of seizures were also reported in study COV3009, which were balanced between Ad26.COV2.S and placebo (3 on each group). All events were non-serious and considered as not related to study vaccination. No events of seizures were reported in other clinical trials up to the DLP.

A total of 226 cases of seizures were received from post marketing sources until the DLP of 24 August 2021. Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is consistent wth what is currently known about the occurrence of convulsions/seizures from the clinical trials data. A review of the results for the US and EU broad analysis Observed versus expected analysis in EU and US did not raise any concern.

In conclusion, based on the cumulative analysis of all available data, no safety concern has been identified for seizure/convulsions. In COV3001, from the 12 potential TTS cases in the Ad26.COV2.S group (in 11 subjects), there were 6 classified as possible according to the specified definition criteria (including 1 assessed as related to the study vaccine by Investigator), and 1 confirmed case of TTS (but considered as non-related). From the 6 potential TTS cases in the Placebo crossover to Ad26.COV2.S group (in 2 subjects), 3 were classified as possible according to the definitioncriteria (none of them were assessed as related to the study vaccine by Investigator). TTS is a recognised adverse drug reaction for Ad26.COV2.S.

5.8. Study COV3009

5.8.1. Methods

VAC31518COV3009 is an ongoing, multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults 18 years of age or older. The efficacy, safety, and immunogenicity of Ad26.COV2.S is being evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine. The planned total sample size was up to approximately 30,000 participants.

In the double-blind phase, participants were randomized in a 1:1 ratio to receive either 2 doses of Ad26.COV2.S or placebo with a 56-day interval. The study vaccines were administered by intramuscular injection in the deltoid muscle. Ad26.COV2.S was administered at a dose level of 5×10^{10} vp.

Following EUA and/or conditional licensure for the single dose schedule, based on the VAC31518COV3001 primary analysis results, all participants from countries where protocol amendment 4 was approved by Health Authority and IEC/IRB were gradually unblinded and the unblinded participants entered the open-label part of the study. After unblinding, a single dose of Ad26.COV2.S was offered to enrolled participants who initially received placebo and enter the open-label vaccination phase of the study while participants from the Ad26.COV2.S arm continued in the same arm to receive their second active dose, if applicable.

A total of 31,300 participants were randomized and vaccinated in the double-blind phase of the study (15,708 in the Ad26.COV2.S group and 15,592 in the placebo-group). During the double-blind phase, 14,549 (46.5%) participants received only one dose of study vaccine (7,053 received Ad26.COV2.S and 7,496 received placebo) and 16,751 (53.5%) participants received two doses of study vaccine (8,655 received Ad26.COV2.S and 8,096 received placebo).

At the data cut-off for this analysis (25 June 2021), 71.2% and 28.4% of participants had completed 2 months of follow-up after the first and booster vaccinations, respectively.

Summaries of deaths, SAEs, MAAEs, AESIs, and AEIs are based on the FAS (31,300 participants; 15,708 in the Ad26.COV2.S group and 15,592 in the placebo group at dose 1). In the FAS, the overall median exposure time in the Ad26.COV2.S group was: 71 days after the first vaccination and 38 days after second vaccination.

Summaries of solicited and unsolicited AEs are based on the Safety subset (ie, a subset of the FAS), which included 6,068 participants (3,016 in the Ad26.COV2.S group and 3,052 in the placebo group) for dose 1. For dose 2, the Safety subset contains 1,559 participants in the Ad26.COV2.S group and

1,425 participants in the placebo group. Overall, 71.1% of the subjects have completed 2 months follow-up after 1st vaccination. After the 1st dose, the median follow-up is 72 days for all subjects (in Ad26.COV2.S and placebo groups). After the 2nd dose 56 days after dose 1, the median follow-up is 40 days for all subjects (in both groups).

Topline (TLR) results for the double-blind phase have been submitted (data cutoff: 25 June 2021).

5.8.2. Results

5.8.2.1. Demographic and baseline characteristics

Overall in the FAS, 76.4% of participants were white and were mainly coming from Europe (41%) and United States (38.9%). 52.6% of participants were males. The median age was 53 years (range: 18; 99 years) and 35.9% of participants were ≥60 years of age. The median BMI was 26.6 kg/m^2 (range: 14-73.2 kg/m^2). 41.4% of subjects had at least 1 comorbidity at baseline; The main comorbidity being obesity (25.7% of subjects). There were 1,791 participants with positive SARS-CoV-2-Serostatus and/or PCR status at baseline in the 5.10^{10} vp group and 1,756 in the placebo group.

Demographic characteristics were similar in the Safety subset. There were 337 participants with positive SARS-CoV-2-Serostatus and/or PCR status at baseline in the 5.10^{10} vp group and 337 in the placebo group. No relevant differences in demographics and baseline characteristics were observed between the Ad26.COV2.S group and the placebo-group in any of the predefined analysis sets.

Details about intake of concomitant medications have been provided. In the FAS, analgesics/antipyretics were used by 1,065 (6.8%) participants in the Ad26.COV2.S and 360 (2.3%) participants in the placebo group up to 7 days post-vaccination. The most frequently used analgesics/antipyretics were paracetamol and ibuprofen with a frequency that was higher in participants in the Ad26.COV2.S group, compared to participants in the placebo group. More participants used analgesics/antipyretics after the first vaccination with Ad26.COV2.S (5.5%) than after the second vaccination with Ad26.COV2.S (4.1%) (in placebo: 1.6% post-dose 1 and 1.6% post-dose 2).

Corticosteroids were used by approximately 3.2% to 3.5% of participants in both the active and placebo group during the 28-day post-vaccination periods (with similar frequencies post-dose 1 and post-dose 2).

In the safety subset,more participants in the Ad26.COV2.S group reported the use of medication as compared to placebo (20.4% versus 7.6%) mainly driven by the use of medication in the context of treatment of solicited symptoms. The use of medication was similar after the booster dose (second dose) compared to the first dose in both groups (16.7% post-dose 1 and 15.6% post-dose 2 in Ad26.COV2.S group, and 5.6% post-dose 1 and 5.3% post-dose 2 in placebo group).

5.8.2.2. Solicited AEs

In general, the overall frequencies for local and systemic solicited AEs were similar post dose 1 versus post dose 2 of 5x10^{10} vp Ad26.COV2.S (2 months apart). As expected, the frequencies for local and systemic solicited AEs were higher in the Ad26.COV2.S group compared to the placebo-group post dose 1 and post dose 2. In both groups, the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment.

Solicited local AEs

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, compared to participants in the placebo group, and with a frequency similar post-dose 1 (54.2% and 18.2%, respectively) and post-dose 2 (56.3% and 15.8%, respectively) (mainly grade 1 and 2).

All solicited local AEs were transient in nature and reported as resolved. Grade 3 solicited local AEs were reported in 19 (0.6%) participants in the Ad26.COV2.S group, post-dose 1 (0.3%) and post-dose 2 (0.6%). No Grade 4 solicited local AEs were reported.

A general trend for lower reactogenicity in both Ad26.COV2.S and the placebo groups, was observed inadults 60 years of age and older compared to adults 18-59 years.

Local reactogenicity was transient, with a median duration of 2-3 days after vaccination with Ad26.COV2.S.

Solicited systemic AEs

The most frequently reported solicited systemic AEs were fatigue, headache, and myalgia. The frequencies of all solicited systemic AEs were slightly higher post-dose 1 compared to post-dose 2 in the Ad26.COV2.S group: fatigue (44.9% vs. 41.1%, respectively), headache (42.8% vs. 35.8%), myalgia (38.9% vs. 34.7%), nausea (18.1% vs. 14.4%) and pyrexia (5% vs. 2.4%). However, this trends is also observed in the placebo group: fatigue (24.9% vs. 20.6%, respectively), headache (24.5% vs. 18.9%), myalgia (15.3% vs. 13.1%), nausea (10.4% vs. 7%) and pyrexia (0.5% vs. 0.3%).

The frequency of solicited systemic AEs was higher in participants in the Ad26.COV2.S group, compared to participants in the placebo group (post-dose 1 and post-dose 2). Most solicited systemic AEs were transient in nature and reported as resolved. Grade 3 solicited systemic AEs were reported in 76 (2.5%) participants in the Ad26.COV2.S group, post-dose 1 (1.8%) and post-dose 2 (1.6%). No Grade 4 solicited systemic AEs were reported.

A general trend for lower reactogenicity in both Ad26.COV2.S and the placebo groups was observed in adults 60 years of age or older compared to adults 18-59 years of age.

Systemic reactogenicity was transient, with a median duration of 1-2 days after vaccination with Ad26.COV2.S.

5.8.2.3. Unsolicited AEs

Overall, in the safety subset, unsolicited AEs were reported for 18.6% of participants in the Ad26.COV2.S group and 13.7% of participants in the placebo group. In both groups, the frequency of unsolicited AEs was slightly higher after the 1st (15.1% and 10.9%, respectively) compared to the 2nd dose (10.2% and 8.4%) (2 months apart) (mainly grade 1 and 2). In both groups, the frequency of unsolicited AEs considered related to the study vaccine was slightly higher after the 1st (9.4% and 5.9%, respectively) compared to the 2nd dose (5.1% and 3.4%). There were no fatal AE. In the Ad26.COV2.S group, the frequencies of SAE were similar post-dose 1 (8 subjects – 0.3% including 1 considered related to vaccine) and post-dose 2 (2 subjects – 0.1%; none considered related to

vaccine). In the placebo group, the frequencies of SAE were similar post-dose 1 (7 subjects – 0.2%; none considered related to vaccine) and post-dose 2 (2 subjects – 0.1%; none considered related to vaccine).

In the Ad26.COV2.S and the placebo groups, the most frequently reported unsolicited AEs, which were also recorded as solicited AEs, were headache, fatigue, and myalgia, with slightly higher frequencies post-dose 1 compared to post-dose 2:

- Ad26.COV2.S group: headache (3.5% post-dose 1 and 2.2% post-dose 2), fatigue (3.5% and 1.9%, respectively), and myalgia (2.7% and 1.4%, respectively)
- Placebo group: headache (3.2% post-dose 1 and 1.8% post-dose 2), fatigue (3.1% and 2%, respectively), and myalgia (2.2% and 1.5%, respectively)

In the Ad26.COV2.S and the placebo groups, the most frequently reported unsolicited AEs that were not recorded as solicited AEs were chills and arthralgia, with slightly higher (or similar) frequencies post-dose 1 compared to post-dose 2:

- Ad26.COV2.S group: chills (0.7% post-dose 1 and 0.5% post-dose 2), and arthralgia (0.6% and 0.4%, respectively)
- Placebo group: chills (0.2% post-dose 1 and 0.1% post-dose 2), and arthralgia (0.2% and 0.2%, respectively)

Numerical imbalances with higher frequencies in the Ad26.COV2.S group versus the placebo group were observed for the following unsolicited AEs:

- Tonsilitis was reported for 2 (0.1%) versus 0 participants post-dose 1 and 3 (0.2%) versus 0 participants post-booster dose (second dose). The sponsor considers that no biological plausibility is established and that it is unlikely that these events were associated with Ad26.COV2.S vaccination. No numerical imbalances for tonislitis were observed in study COV3001.
- Feeling abnormal was reported for 10 (0.3%) versus 9 (<0.3%) participants post-dose 1 and 3 (0.2%) versus 0 participants post-booster dose (second dose). Symptoms reported as 'feeling abnormal' are unspecific symptoms. One of the reported terms was 'brain fog' associated with dizziness, which is already listed as an adverse drug reactions in the product information. No numerical imbalances were observed in study COV3001 (feeling abnormal reported for 6 participant in the Ad26.COV2.S group compared to 5 in the placebo group).
- Abdominal pain was reported for 12 (0.4%) versus 4 (0.1%) participants post-dose 1 and 3 (0.2%) versus 0 participants post-booster dose (second dose). Decreased appetite was reported for 11 (0.4%) versus 6 (0.2%) participants post-dose 1 and 1 (0.1%) versus 1 (0.1%) participants post-booster dose (second dose). Both abdominal pain and decreased appetite were in several cases co-reported with diarrhoea. Diarrhoea is already listed as an adverse drug reaction.

Overall, these numerical imbalances do not raise any new safety concern for the Ad26.COV2.S vaccine.

AEs of at least Grade 3 in severity were reported for 0.7% and 0.8% of participants in the Ad26.COV2.S group post-dose 1 and post-booster dose (second dose), respectively (vs. 0.5% and 0.5%, respectively, in placebo group). Post-dose 1, the most frequently reported unsolicited AE of at least Grade 3 in severity was headache (0.3%) (0.1% in placebo group). Post-booster dose (second dose), nausea (2 participants [0.1%]) was the only unsolicited AE of at least Grade 3 in severity reported for more than 1 participant (0% in placebo group).

Unsolicited AEs related to vaccination were reported for 9.4% and 5.1% of participants in the Ad26.COV2.S group post-dose 1 and post-booster dose (second dose), respectively (vs. 5.9% and

3.4%, respectively, in placebo group). In both groups, the most frequently reported unsolicited AEs related to vaccination were fatigue (2.7% and 1.4% in Ad26.COV2.S group; 2.4% and 1.5% in placebo group) and headache (2.6% and 1.4% in Ad26.COV2.S group; 2.2% and 1.2% in placebo group) which are both recognised adverse drug reaction for Ad26.COV2.S.

5.8.2.4. Immediate Adverse Events

Solicited and unsolicited immediate AEs were infrequent (<0.5% of participants post-dose 1 or post-booster dose (second dose). Immediate hypersensitivity reactions following vaccination were rare and non-serious. No immediate severe allergic (anaphylaxis) reactions were reported. Anxiety-related reactions to vaccination, including vasovagal reactions such as syncope and presyncope, were rare (<0.1%), and evenly distributed between the Ad26.COV2.S and placebo groups post-dose 1 and post-booster dose (second dose).

5.8.2.5. Fatal AEs and SAEs

Fatal AEs

Up to the cut-off date of 25 June 2021, in the FAS, 17 fatal AEs were reported during the **double-blind phase:** 4 in the Ad26.COV2.S group and 13 in the placebo group.

Of the 4 deaths reported in the **Ad26.COV2.S group**, none had a SARS-CoV-2 positive test during the study. The causes of death by preferred term were lung adenocarcinoma and death of unknown cause after the first dose, and, after the booster dose (second dose), cerebral haemorrhage (13 days after 2nd injection) and myocardial infarction (41 days after 2nd injection) all of which were considered not related to vaccination by investigator assessment.

In the placebo group, 6 of the 13 deaths had a positive SARS-CoV-2 test during the study, and the causes of death in these participants were COVID-19 or COVID-19 pneumonia.

There were 5 fatal cases that occurred between the data cut-off (25 June 2021) and database lock (DBL) (23 August 2021) in participants who received Ad26.COV2.S in COV3009: myocardial infarction 117 days after the booster dose (second dose) (possible TTS case), grade 4 bilateral COVID positive phenumonia with hypoxemia 51 days after booster dose (second dose), stage 4 breast cancer 129 days after vaccination with the first dose, unspecificed death in a 50-59 year old participant 162 days after vaccination and one unspecified death in an over 85 year old participant at an unknown time after vaccination. All these events were considered not related to vaccination by the investigator.

When considering the double-blind and open-label phases combined, 26 deaths were reported up to the cutoff date of 25 June 2021, of which 10 occurred in participants who received Ad26.COV2.S (1 chronic obstructive pulmonary disease, 1 cerebral haemorrhage, 1 COVID-19 pneumonia, 1 overdose of heroin, 1 lung adenocarcinoma, 3 myocardial infarction and 2 deaths from unknown causes). None of these deaths were considered related to the study vaccine by the investigator. Only 1 death in the placebo group was considered related to the study vaccine by the investigator but not related by the sponsor. This participant was enrolled in the placebo group and received after unblinding an open-label vaccination with the Ad26.COV2.S vaccine 36 days after receiving the initial placebo vaccination. This participant was reported with a Grade 4 SAE of respiratory distress on the night of receiving the open-label Ad26.COV2.S vaccine. The same day, the participant was admitted to the hospital, where the participant passed away 28 days later. Underlying cause of death was acute respiratory distress syndrome due to COVID-19 pneumonia.

SAEs

In the double-blind phase of the study, SAEs were reported for 240 participants in the FAS (104 [0.7%] participants in the Ad26.COV2.S group and 136 [0.9%] participants in the placebo group). A total of 98 (0.6%) participants reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared to 104 (0.7%) participants in the placebo group. A total of 8 (0.1%) participants reported SAEs associated with COVID-19 in the Ad26.COV2.S group compared with 36 (0.2%) participants in the placebo group.

No increase in the frequency of SAEs (all and those not associated with COVID-19) was observed post-booster dose (second dose) compared with post-dose 1 Among the SAEs not associated with COVID-19, no significant numerical imbalances were observed in the Ad26.COV2.S by system organ class.

Among all SAEs reported during the double-blind phase, excluding COVID-19 associated events, 11 participants experienced a total of 13 SAEs that were considered related by investigator assessment (8 [0.1%] participants in the Ad26.COV2.S and 3 [<0.1%] participants in the placebo group). In the Ad26.COV2.S group after the first dose, the related SAEs were pyrexia, pericarditis, allergy to vaccine, and hemoptysis in 1 participant each, and injection site swelling, vertigo, and myocardial necrosis marker increased in 1 participant. Related SAEs after the blinded booster dose (second dose) were facial paresis, pulmonary embolism, and cerebrovascular accident in 1 participant each. Only the SAE of allergy was considered related to the study vaccine by the MAH.

In the pooled analysis, including double-blind and open label phase, among all participants who received Ad26.COV2.S during the study, 4 additional participants reported a total of 6 SAEs considered related by the investigator: cerebrovascular accident / stroke 30 days after 2nd dose of active vaccine; thrombocytopenia and leukopenia 86 days after 1st dose of active vaccine, and cellulitis of the right leg and deep vein thrombosis 99 days after 1st dose of active vaccine; thrombosis of the vena saphena magna of the right leg 58 days after the booster dose (second dose) of active vaccine; thrombosis of the right leg 20 days after the booster dose (second dose) of active vaccine. All these SAEs were considered as not related by the MAH.

5.8.2.6. Medically-attended Adverse Events

In the double-blind phase of the study, at least 1 MAAE was reported for 1,033 (6.6%) participants in the Ad26.COV2.S group and 1,003 (6.4%) participants in the placebo group (no increase in the frequency of MAAEs was observed post-booster (second dose) compared with post-dose 1).

The frequency of subjects with ≥ grade 3 MAAEs was similar in Ad26.COV2.S (157 – 1%) and placebo groups (191 – 1.2%).

Slightly more participants had 1 or more related MAAEs not associated with COVID-19 in the Ad26.COV2.S group (92 [0.6%]) than the placebo group (47 [0.3%]). The most frequently reported related MAAEs not associated with COVID-19 in the Ad26.COV2.S group were headache (10 [0.1%] participants) and fatigue (9 [0.1%] participants).

5.8.2.7. AEs leading to discontinuation

Three participants reported AEs resulting in study discontinuation in the double-blind phase (safety subset): 1 (urticaria) in the Ad26.COV2.S group and 2 (COVID-19) in the placebo group. Six participants reported AEs resulting in study treatment discontinuation: 1 (urticaria) in the Ad26.COV2.S groups and 5 (COVID-19 infection/pneumonia) in the placebo group.

During the entire study (FAS), up to the cutoff date of 25 June 2021, 5 participants in the

Ad26.COV2.S group and 10 participants in the placebo group discontinued the study due to an AE (one event occurred after unblinding). Two events were considered related: 1 in the Ad26.COV2.S group (Grade 3 AE of urticaria reported 6 days post-dose 1) and 1 in the placebo group (Grade 1 AE of ventricular extrasystoles reported 27 days post-dose 1). Thirty AEs leading to treatment discontinuation were reported in 28 participants in the Ad26.COV2.S group, of which 2 events were reported after unblinding. In the placebo group, 44 AEs leading to treatment discontinuation were reported in 35 participants, of which 3 events were reported after unblinding. Ten events in the Ad26.COV2.S group that led to study treatment discontinuation were considered related.

5.8.2.8. AESIs

Thrombosis with thrombocytopenia syndrome (TTS) is a recognised adverse drug reaction (frequency very rare) in the product information of Ad26.COV2.S following the assessment of a safety signal from post-marketing data. TTS was considered an AESI and is closely monitored in all available sources, including clinical studies. A thrombotic event or thrombocytopenia (defined as platelet count below 150,000/µL [Brighton 2021]) alone was considered a suspected AESI for further investigation.

In the double-blind phase of the COV3009, at least 1 suspected AESI (thrombotic event or thrombocytopenia) was reported for 18 (0.1%) participants in the Ad26.COV2.S group (13 participants after the first dose and 5 participants after the booster dose (second dose)) and 22 (0.1%) participants in the placebo group. The majority were thromboembolic events, reported for 14 (0.1%) participants in the Ad26.COV2.S group and 18 (0.1%) participants in the placebo group. Thrombocytopenia was reported as a suspected AESI for 4 (<0.1%) participants in the Ad26.COV2.S group and 5 (<0.1%) participants in the placebo group.

Additional detail on possible TTS cases is provided below:

In the placebo group:

- a 50-59 year-old subject had cerebrovascular accident and hemiparesis on Day 36. The case met the PRAC criteria of a possible case of TTS and was considered as not related to the blinded study vaccine.
- a 60-69 year-old subject had deep vein thrombosis on Day 27 (double-blind phase) and subsequently pulmonary embolism on Day 29 (open-label phase) in combination with thrombocytopenia. The case met the PRAC criteria of a possible case of TTS and was considered as not related to the blinded study vaccine.
- a 50-59 year-old subject who developed myocardial infarction and peripheral artery thrombosis 68 and 78 days, respectively, after the first vaccination (criteria not meet according to PRAC criteria and considered as not related to the blinded study vaccine).

In the Ad26.COV2.S group:

- Deep vein thrombosis in combination with thrombocytopenia was reported for 1 participant in the Ad26.COV2.S group 100 days post-vaccination 1 (60-69 year-old subject). This participant was unblinded before the event and is therefore counted in the open-label phase. The case met the PRAC criteria of a possible case of TTS, and was considered as related to study vaccine by Investigator.
- Subject was a 60-69 year-old who developed myocardial infarction (fatal). The serious event of myocardial infarction occurred 175 days after the first vaccination and 118 days after the second vaccination. Non serious thrombocytopenia was reported. The case met the PRAC criteria of a possible case of TTS, and the Investigator considered the event of myocardial infarction not related

to the blinded study vaccine (in particular because of the too long time-to-onset).

During the double-blind phase, numerical imbalances were observed for the following adverse events of interest: rash (35 [0.2%] participants in the Ad26.COV2.S group versus 22 [0.1%] participants in the placebo group), urticaria (16 [0.1%] participants in the Ad26.COV2.S group versus 7 [<0.1%] participants in the placebo group), tinnitus (9 [0.1%] participants in the Ad26.COV2.S group versus 5 [<0.1%] participants in the placebo group), and Bell's Palsy (2 [<0.1%] participants in the Ad26.COV2.S group versus 0 participants in the placebo group). No notable numerical imbalance between the Ad26.COV2.S group and placebo group was observed for facial paralysis (3 versus 2 cases). Two of the 3 facial paralysis cases in the Ad26.COV2.S group were Bell's palsy, which both occurred after the first dose. The third case was facial paresis, which occurred post-booster dose (second dose).

No trends for numerical imbalances were observed for convulsions/seizures, deep vein thrombosis, pulmonary embolism, myocarditis, or pericarditis. No cases of GBS, capillary leak syndrome (CLS), or encephalitis were reported during the double-blind phase. In the double-blind phase, arterial embolic and thrombotic events were reported for fewer participants in the Ad26.COV2.S group than placebo group (6 versus 9).

TTS, venous thromboembolism, rash, and urticaria, and tinnitus are recognized ADRs in the SmPC. Bell's palsy, acute aseptic arthritis and non-haemorrhagic stroke are AESIs in the RMP and are being closely monitored.

During the double-blind phase, the reporting rate of arthritis in the Ad26.COV2.S group was higher compared to the placebo group (38 [0.2%] vs 22 [0.1%] cases). The majority of the events occurred post-dose 1 (24 [0.2%] versus 12 [0.1%] cases in the 28-day period post-dose 1); fewer events were observed in the 28-day period post-dose 2 (4 [<0.1%] versus 5 [0.1%] cases). The events reported in the category of arthritis in the Ad26.COV2.S group included arthritis, osteoarthritis, periarthritis, gout, spinal osteoarthritis, gouty arthritis, and oligoarthritis. During the double-blind phase, SAEs in the category of arthritis were reported for 4 participants in the study (2 in the Ad26.COV2.S group and 2 in the placebo group), all of which were considered not to be related to vaccination. In the Ad26.COV2.S group, SAEs of sub-acromioclavicular osteoarthritis and worsening osteoarthritis were reported for 1 participant each 16 and 50 days, respectively, after the first dose. In the placebo group, 2 participants had SAEs of worsening osteoarthritis. Two nonserious AEs in the category of arthritis were considered related to vaccination: gout flare reported 8 days after the first vaccination and oligoarthritis reported 13 days after the first vaccination, both of which were reported for participants in the Ad26.COV2.S group. In study COV3001, these imbalances were not observed (reported for 40 [0.2%] participants in the Ad26.COV2.S groups compared to 42 [0.2%] in the placebo group during the double-blind phase) and post-marketing monitoring did not raise any safety signal or concern for arthritis.

The majority of participants with these events had previous history of Arthritis or osteoarthritis. The main numerical difference was in gout and gouty arthritis with 8 events in the Ad26.COV2.S group and 1 event in Placebo. All participants except one participant in the Ad26.COV2.S group had medical history of Gout or predisposing factors. There were 8 participants with AEs of periarthritis, 6 in the Ad26.COV2.S group and 2 in the placebo group, most with a history of such events. All events in the Ad26.COV2.S group involved shoulder and one involved wrist. For immune mediated arthritis, there was one event in the placebo group (Psoriatic Arthropathy).

Since launch till 24 August 2021, 243 cases reporting acute aseptic arthritis from post-marketing sources were identified. These 243 cases reported 250 events of interest (61 serious, 189 non-serious) and the most frequently reported country of origin was the Republic of Korea (n=124). Of the 243 cases, 125 concerned males, 106 females, and 12 had no sex reported. The age range was 19 to 84 years. The most commonly reported preferred terms (n⩾2) included arthritis (n=173), rheumatoid arthritis (n=27), gout (n=12), periarthritis (n=10), 4 each of osteoarthritis and spinal osteoarthritis, 3 each of temporomandibular joint syndrome, facet joint syndrome, Still's disease, and 2 each of acute aseptic arthritis, polyarthritis, and rheumatic disorder. The mean and median time to onset was 6.4 days and 2 days, respectively. Where reported (n=118), the outcomes were reported as not resolved (n=62), resolved (n=38), resolving (n=17), and resolved with sequelae (n=1). A broad O/E analysis for the US and EU and the sensitivity analysis showed an O/E ratio of <1 in the US and EU for both age groups. A restricted O/E analysis was not required.

In conclusion, although a numerical imbalance has been observed in COV3009, this finding was not replicated in the other large phase 3 study COV3001. No signal has been identified from post-marketing experience

During the double-blind phase, hemorrhagic disorders reported for a low percentage of participants in the Ad26.COV2.S group and the placebo group (55 [0.4%] versus 29 [0.2%], respectively). This was also observed between the Ad26.COV2.S group and placebo group in the 28 days post-dose reporting period (24 [0.2%] versus 14 [0.1%] cases post-dose 1, and 17 [0.2%] versus 7 [0.1%] cases post-dose 2). This included 6 [<0.1%] SAEs in the Ad26.COV2.S group: cerebral haemorrhage, worsening of haemorrhagic ovarian cyst, haemothorax, upper gastrointestinal bleed and urethral bleeding, which were considered not related to vaccination, and a related event of hemoptysis which occurred 66 days post dose 1. In the placebo group, 2 [<0.1%] SAEs of gastrointestinal haemorrhage and lower gastrointestinal bleed were reported, both of which were considered not related to vaccination. When considering the 28 days post-dose reporting period, SAEs of hemorrhagic disorders were reported for 1 (<0.1%; worsening of haemorrhagic ovarian cyst) versus 1 (<0.1%; lower gastrointestinal bleed) participants after the first dose and 2 (<0.1%; urethral bleeding and cerebral haemorrhage) versus 0 participants post-booster dose (second dose) in the Ad26.COV2.S group versus the placebo group. At the high-level term, the numerical imbalances let to the assessment in more depths of the events at the system organ class level. Disregarding events related to trauma, injury, or injection site AEs, no imbalances were seen for any system organ class within the 28 days post each dose. Injury was reported in 13 participants in the Ad26.COV2.S group compared to 4 in the placebo group. This imbalance is mainly driven by contusion due to injury (9 versus 2), none were injection site related. Platelet counts are not available for these hemorrhagic events as there were no safety laboratory samples collected in study COV3009. In study COV3001, this imbalance was not observed for the Ad26.COV2.S group versus the placebo group in COV3001 for the primary analysis (22 [0.1%] versus 25 [0.1%]) or final analysis (48 [0.2%] versus 77 [0.4%]) of the double-blind phase.

5.9. Study DMID 21-0012

5.9.1. Methods

This is an is an ongoing Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines (conducted by NIH/NIAID in the US).

The MAH submitted the Safety Monitoring Committee report (SMCR), where only data from Groups 4E,

5E and 6E of Cohort 1 are presented (data cut-off date: 24 September 2021): homologous or heterologous booster vaccination with Ad26.COV2.S 5×10^{10} vp at least 12 weeks after primary vaccination with an approved mRNA COVID-19 vaccine regimen (2 doses of Moderna-mRNA-1273 or Pfizer/BioNTech-BNT162b2) or Ad26.COV2.S 5×10^{10} vp.

All the data discussed here has been collected under Versions 2.0-4.0 of the protocol (*not submitted*). Persons who have previously received COVID-19 vaccine under EUA dosing guidelines, completing their regimen at least 12 weeks prior to enrolment, were recruited in cohort 1. Each participant in Cohort 1 is followed for approximately 1 year and is expected to complete 7 visits.

A total of 150 participants have been enrolled into Groups 4E to 6E of Cohort 1, all receiving the Janssen Ad26.COV2.S booster vaccination at the 5×10^{10} vp dose level: 50 participants in **Group 4E** (EUA Dosed Janssen Ad26.COV2.S), 49 participants in **Group 5E** (EUA Dosed Moderna mRNA-1237) and 51 participants in **Group 6E** (EUA Dosed Pfizer/BioNTech BNT162b2). All 150 enrolled participants received the study delayed boost vaccination, all 150 participants have remained in the study and no discontinuations have been reported. All participants had completed the Day 14 visit and 148 (98.7%) had completed the Day 29 visit (after booster vaccination). No participants in these groups have yet reached Day 91 or later visits.

The mean delay between the last primary dose and Janssen booster vaccination was 17.7 weeks after Janssen primary vaccination, 19.3 weeks after second dose of Moderna and 20.6 weeks after the second dose of Pfizer.

5.9.2. Results

5.9.2.1. Demographic and baseline characteristics

Of the 150 enrolled participants, most (84.7%) were white and 56.0% were male. Half (50.0%) of the participants were between 18- and 55 years of age, and half (50.0%) were at least 56 years of age with a median age of 55.0 years (range 20-77). The median BMI was 26.9 kg/m^2 (range 17.0-46.5 kg/m^2).

Overall, these characteristics were similar in each group. However, there were more male in group 5E (67.3%) vs. group 6E (54.9%) vs. group 4E (46%). And there were more Asian in groups 5E (10.2%) and 6E (11.8%) vs. group 4E (6%).

5.9.2.2. Solicited AEs

The most frequently reported solicited local AE was pain and/or tenderness reported in 108 (72.0%) participants with similar frequencies in each group: 37 (74%) in group 4E, 35 (71.4%) in 5E, and 36 (70.6%) in 6E. Erythema/redness (11.3%) and induration/swelling (10.7%) were reported slightly less frequently in group 5E compared to 4E and 6E: 2 (4.1%) and 2 (4.1%), respectively, in 5E; 7 (14%) and 9 (18%) in 4E; 8 (15.7%) and 5 (9.8%) in 6E.

All were Grade 1 or 2 in severity, except for 1 local solicited event of Grade 3 pain and/or tenderness reported on Day 3 in group 5E. No Grade 4 events were reported.

All solicited systemic AE were less frequently reported in group 4E compared to groups 5E and 6E (in particular chills and fever).

The most frequently reported solicited systemic AE were malaise and/or fatigue reported in 107 (71.3%) participants: 31 (62%) in group 4E, 38 (77.6%) in 5E, and 38 (74.5%) in 6E. Myalgia were reported in 88 (58.7%) participants: 25 (50%) in group 4E, 32 (65.3%) in 5E, and 31 (60.8%) in 6E. Headache were reported in 72 (48%) participants: 24 (48%) in group 4E, 25 (51%) in 5E, and 23 (45.1%) in 6E. Chills were reported in 49 (32.7%) participants: 9 (18%) in group 4E, 23 (46.9%) in 5E, and 17 (33.3%) in 6E. Arthralgia were reported in 47 (31.3%) participants: 10 (20%) in group 4E, 17 (34.7%) in 5E, and 19 (37.3%) in 6E. Nausea were reported in 31 (20.7%) participants: 9 (18%) in group 4E, 12 (24.5%) in 5E, and 10 (19.6%) in 6E. Fever were reported in 30 (20%) participants: 3 (6%) in group 4E, 16 (32.7%) in 5E, and 11 (21.6%) in 6E.

Most solicited systemic AEs were Grade 1 or 2 in severity. There were no ≥ grade 3 solicited systemic AEs in group 4E. In group 5E, there were 3 severe malaise and/or fatigue, 3 severe myalgia, 4 severe headache, 3 severe nausea, 3 severe chills, 1 severe arthralgia and 3 severe fever. In group 6E, there were 1 severe malaise and/or fatigue, 2 severe myalgia, 1 severe headache, 1 severe nausea, 2 severe chills, 2 severe arthralgia and 1 severe fever. No Grade 4 events were reported.

5.9.2.3. Unsolicited AEs

In Group 4E, 18 participants (36%) reported 32 unsolicited AEs (all grade 1). In group 5E, 15 participants (30.6%) reported 29 unsolicited AEs (22 grade 1, 4 grade 2, 2 grade 3 and 1 grade 4). In Group 6E, 20 participants (39.2%) reported 38 AEs (31 grade 1, 5 grade 2 and 2 grade 3).

A total of 18 (12.0%) participants reported 1 or more unsolicited AEs related to study vaccination, most of which were Grade 1 or 2 in severity. The number (and percentage) of participants reporting unsolicited AEs, of any severity grade, that were deemed related to the study product was 3/50 (6.0%) in Group 4E (contusion, back pain, and dizziness), 7/49 (14.3%) in Group 5E (lymphadenopathy, diarrhoea, vomiting, axillary pain, fatigue, feeling abnormal, swelling, memory impairment, migraine, insomnia, stress oropharyngeal pain) and 8/51 (15.7%) in Group 6E (lymphadenopathy, 2 feeling abnormal, injection site bruising, injection site reaction, gout, 2 dizziness, 2 insomnia, oropharyngeal pain).

For 3 (2.0%) participants (2 in Group 5E and 1 in Group 6E), 4 related AEs of Grade 3 were reported (vomiting, fatigue/feeling abnormal, and insomnia). No related Grade 4 events were reported.

No deaths were reported. In group 5E, 1 SAE of Grade 4 acute cholecystitis was reported on Day 25 (Atmar 2021). The event was considered not related to the study vaccine and was reported as resolved. In the same group, 1 Grade 3 event of vomiting was considered related to Ad26.COV2.S. The event was not reported as an SAE and resolved after 2 days.

5.9.2.4. AEs leading to discontinuation

No AE leading to early termination of the study and no discontinuations have been reported in either group.

5.9.2.5. AESIs

In group 5E, 1 AESI has been reported: Grade 3 event of vomiting, related to Ad26.COV2.S. The event was not reported as an SAE and resolved after 2 days.

5.10. Discussion

The main safety data are from the double-blind phase of the phase 3 study **COV3009**: 8,655 subjects were vaccinated with 2 doses of Ad26.COV2.S 5×10^{10} vp with 2-month interval (FAS); the safety subset includes 1,559 participants in the Ad26.COV2.S group for dose 2.

Supportive data: There were also additional data from the early phase studies for participants received a primary dose and a booster dose (second dose) of Ad26.COV2.S at the 5×10^{10} vp dose level: 418 subjects with a 2-month interval across studies **COV1001, COV1002, and COV2001**; 128 with a 3-month interval across studies COV1001 and COV2001; 19 with a 6-month interval in study COV1001 (and an estimated 159 participants with a 6-month or longer interval in study COV2008 - dose-level blinded data).

Finally, across studies COV1001 and COV1002, 235 participants received 2 doses of 1×10^{11} vp Ad26.COV2.S with a 2- or 3-month interval. Furthermore, 74 participants received a primary dose of 5×10^{10} vp Ad26.COV2.S followed by 1.25×10^{10} vp Ad26.COV2.S booster dose (second dose) 6 months later in COV2001.

In the double-blind phase of COV3009, participants were randomized in a 1:1 ratio to receive either **2 doses of Ad26.COV2.S 5×10^{10} vp or placebo with a 56-day interval**. At the data cut-off for this analysis (25 June 2021), 71.2% and 28.4% of participants had completed 2 months of follow-up after the first and booster dose (second dose) vaccinations, respectively. In the FAS, the overall median exposure time in the Ad26.COV2.S group was: 71d after the 1st vaccination and 38d after 2nd vaccination. In the safety subset (double-blind phase), after the 1st dose, the median follow-up is 72 days for all subjects (in Ad26.COV2.S and placebo groups). After the 2nd dose, the median follow-up is 40 days for all subjects (in both groups).

Summaries of solicited and unsolicited AEs are based on the Safety subset: 3,016 subjects in the Ad26.COV2.S group and 3,052 in the placebo group for dose 1; 1,559 participants in the Ad26.COV2.S group and 1,425 participants in the placebo group for dose 2.

From the day of vaccination until 7 days after each vaccination, the overall frequencies of local solicited AEs were similar post-dose 1 and post-dose 2 (mainly driven by vaccination site pain), and lower in older adults (60 years or older) compared to younger adults (18-59 years) (in both Ad26.COV2.S and placebo groups).

From the day of vaccination until 7 days after each vaccination, overall, the frequencies of systemic solicited AEs were slightly higher post-dose 1 versus post-dose 2 (for the most frequently reported solicited systemic AEs: fatigue, headache, and myalgia; and also for nausea and pyrexia), and lower in older adults (60 years or older) compared to younger adults (18-59 years) (in both groups). In the Ad26.COV2.S group, in younger adults, the frequencies of systemic solicited AEs were higher post-dose 1 versus post-dose 2; while these frequencies were similar post-dose 1 versus post-dose 2 in older adults.

From the day of vaccination until 28 days after each vaccination, the frequencies for unsolicited AEs (all and those considered related) were slightly higher post-dose 1 versus post-dose 2 (in both Ad26.COV2.S and placebo groups). The most frequently reported unsolicited AEs that were not recorded as solicited AEs were chills and arthralgia (both recognized ADRs in the SmPC of Ad26.COV2.S).

In the double-blind phase, overall, both in the active treatment arm and in the placebo arm, less adverse events (solicited and unsolicited) are reported after the booster dose (second dose). However, underreporting of adverse events post-dose 2 is unlikely as this trend is also observed in other clinical

trials.

Summaries of deaths, SAEs, MAAEs, and AESIs are based on the FAS (from the day of first vaccination until the end of the study): 15,708 in the Ad26.COV2.S group and 15,592 in the placebo group at dose 1; 8,655 subjects in the Ad26.COV2.S group and 8,096 in the placebo group at dose 2. During the double-blind phase, 17 fatal AEs were reported: 4 in the Ad26.COV2.S group (2 after dose 1 and 2 after dose 2; all considered as not related to vaccine) and 13 in the placebo group.

SAEs (including COVID-19 associated events) were reported for 104 participants in the Ad26.COV2.S group (0.7%) and 136 participants in the placebo group (0.9%). No increase in the frequency of SAEs was observed post-booster dose (second dose) compared with post-dose 1 (in both groups). Eleven participants experienced a total of 13 SAEs that were considered related: 8 participants in the Ad26.COV2.S (0.1%) and 3 participants in the placebo group (<0.1%). In the Ad26.COV2.S group after the first dose, the related SAEs were pyrexia, pericarditis, allergy to vaccine, and hemoptysis in 1 participant each, and injection site swelling, vertigo, and myocardial necrosis marker increased in 1 participant. Related SAEs after the blinded booster dose were facial paresis, pulmonary embolism, and cerebrovascular accident in 1 participant each.

No increase was observed post-booster dose (second dose) compared with post-dose 1 for MAAEs and AEIs (including AESIs thrombotic event and/or thrombocytopenia).

Finally, more participants in the Ad26.COV2.S group reported the use of medication as compared to placebo (20.4% versus 7.6%). The reported use of medication was mainly driven in the context of treatment of solicited symptoms. The use of medication was similar after the booster dose (second dose) compared to the first dose in both groups.

Across studies COV1001, COV1002, and COV2001, overall, with 2, 3 or 6 months interval between the 2 doses of Ad26.COV2.S 5×10^{10} vp, the frequencies of local (mainly driven by vaccination site pain) and systemic solicited AEs were similar or slightly higher post-dose 1 compared to post-dose 2.

The frequency of solicited AEs ≥ grade 3 was very low, and the majority of the solicited systemic AEs were considered related to the use of the study vaccine as per investigator assessment. The majority of unsolicited AE assessed as related to vaccination are recognized ADR in the SmPC.

Overall, the intake of concomitant medication was similar or higher post-dose 1 compared to post-booster dose (second dose or post-antigen presentation).

A trend towards an increase in the frequency solicited AEs (local and systemic) was observed with increasing vaccine doses (vaccinations with $1.25.10^{10}$ vp, $2.5.10^{10}$ vp, 5.10^{10} vp or 1.10^{11} vp – 2 months apart) (post-dose 1 and post-dose 2), together with an increase of the intake of concomitant medication.

A trend towards a decrease in the frequency and severity of solicited AEs with increasing age of participants was observed post-dose 1 and post-dose 2 Ad26.COV2.S administration (18-30 year-of-age vs. 31-45 vs. 46-55 vs. ≥65 years).

The frequency of unsolicited AEs was overall similar or slightly higher after the 1st compared to the 2nd dose.

In the dedicated booster study COV2008, preliminary dose level-blinded safety data are available from a total of 370 participants (including 7-day reactogenicity data from 244 participants), who have received an Ad26.COV2.S booster dose (second dose) (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) ⩾6 months after primary single-dose Ad26.COV2.S (5×10^{10} vp) vaccination (i.e. in COV3001). Dose level-blinded reactogenicity data are also available from 161 participants (including 7-day reactogenicity data from 76 participants) who have received an Ad26.COV2.S booster dose (second dose) (5×10^{10} vp, 2.5

$\times 10^{10}$ vp, or 1×10^{10} vp) $\geqslant$6 months after primary (2-dose) administration of Pfizer's BNT162b2. However, these data are preliminary and not all participants had completed the 28-day post-vaccination reporting period at the time of the data extraction, and these data are subject to change in further analyses.

Clinical data from **DMID 21-0012 study**, cohort 1, groups 4E, 5E and 6E were also submitted: **homologous or heterologous booster vaccination** with Ad26.COV2.S 5×10^{10} vp at least 12 weeks after primary vaccination with an approved mRNA COVID-19 vaccine regimen (2 doses of Moderna-mRNA-1273 or Pfizer/BioNTech-BNT162b2) or 1 dose of Ad26.COV2.S 5×10^{10} vp. Day 29 after booster vaccination has been reached by most of them, but none have reached day 91. Because of the limited number of subjects in each group (±50), conclusion should not be considered as final.

The most frequently reported solicited local AE (pain and/or tenderness) was reported with similar frequencies in each group. Erythema/redness and induration/swelling were reported slightly less frequently in group 5E (dosed Moderna / boost Janssen) compared to 4E (dosed Janssen/ boost Janssen) and 6E (dosed Pfizer/ boost Janssen).

All solicited systemic AE were less frequently reported in group 4E (dosed Janssen/ boost Janssen) compared to groups 5E (dosed Moderna / boost Janssen) and 6E (dosed Pfizer/ boost Janssen); in particular chills and fever (but also malaise and/or fatigue, myalgia, headache, arthralgia; and nausea).

Overall, unsolicited AEs were reported with similar frequencies in the 3 groups; however, in group 4E, they were all grade 1 (and there were some grade 3 and 4 unsolicited AEs in groups 5E and 6E). Moreover, unsolicited AEs related to study vaccination were reported less frequently in group 4E compared to groups 5E and 6E.

Of note, in Munro et al. 2021, participants primed with Pfizer/Pfizer reported more frequent local and systemic reactions after receiving Moderna, Curevac, Vaxzevria, and Janssen vaccine as a third dose, compared with other vaccines and control. Participants receiving mRNA vaccines or Janssen vaccine after Vaxzevria/Vaxzevria also showed increased systemic and local adverse events. *(Munro et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet December 2021)*

Finally, updated safety clinical data has also been submitted for the **main study COV3001 assessed for the initial conditional MA** after 1 dose of Ad26.COV2.S 5×10^{10} vp (data cutoff: 9 July 2021, instead of initially 22 January 2021). The results from the safety and reactogenicity analyses showed that the 5×10^{10} vp dose level of Ad26.COV2.S administered as a 1-dose regimen had an acceptable safety and reactogenicity profile with no significant safety issues identified versus the initial assessment at time of conditional MA. In general, a lower reactogenicity was observed for the older adults compared with the younger adults.

Risk of TTS

A recent study demonstrates that chimpanzee adenovirus Y25 (ChAdOx1), human adenovirus type 26 (HAdV-D26), and human adenovirus type 5 (HAdV-C5) deployed as vaccination vectors versus SARS-CoV-2 bind to platelet factor 4 (PF4), a protein implicated in the pathogenesis of HIT (heparin-induced thrombocytopenia) *(Baker AT et al. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. Sci Adv. 2021 Dec 3;7(49)*).

For the Janssen COVID-19 vaccine, the estimated reporting rate of TTS in the US is 3.3 per million doses

(assumption that all are after first dose) (CDC, 54 confirmed reports, exposure of 16.4 million, 24/11/2021) and in Germany 6.3 per million doses (PEI, 20 reports, exposure 3.1 million, 26/10/2021)

Ref: CDC: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

PEI:https://www.pei.de/SharedDocs/Downloads/DE/newsroom/dossiers/sicherheitsberichte/sicherheitsbericht-27-12-20-bis-30-09-21.pdf?__blob=publicationFile&v=9

Upon request, the MAH has provided an update of the TTS cases at the DLP of 04 October 2021. A total of 78,047 adult participants had been included in the extended adult pooling, of which 9,177 have received 2 doses of Ad26.COV2.S 5×10^{10} vp (irrespective of interval between doses; unblinded data).

Among the 213 participants with at least 1 event in the SMQ Embolic and thrombotic events, 30 events in 22 participants were identified as Qualified for Assessment TTS events based on platelet count measurements below normal range or with reported thrombocytopenia but unknown actual platelet levels. Of the 30 Qualified for Assessment TTS events, 21 events in 15 participants met confirmed, probable, or possible PRAC requested definition (Table 18). Of these 21 events, 1 event (Ad26.COV2.S; COV3001) was reported with a positive anti-PF4 status (confirmed using PRAC requested definition), and the outcome was fatal for 2 events (Ad26.COV2.S; COV1002, COV3009) (possible using PRAC requested definition).

Table 18: Clinical Trial Qualified for Assessment TTS Events Categorized by PRAC Requested Causality Categories and by Vaccine Received Prior to AE Onset* up to 04 October 2021

PRAC requested criteria	Ad26.COV2.S	Placebo	Cross-vaccinated	Total
Total Qualified for Assessment TTS events	**11**	**14**	**5**	**30****
Confirmed, probable, possible	**8**	**10**	**3**	**21**
Confirmed	1	0	0	1
Probable	0	0	0	0
Possible	7	10	3	20
Unlikely	2	1	0	3
Criteria not met	1	3	2	6

* Excluding events that occurred after date of receiving another COVID-19 vaccine.

** One additional participant experienced "Transient ischaemic attack" after receiving other vaccination outside of the trial (Ad26.COV2.S vaccine, 3 December 2021; Vaccine outside of the trial, 13 January 2021; AE start data, 22 January 2021). Low platelet value was reported in combination with the AE and meets PRAC requested criteria of "possible".

Of the 21 Qualified for Assessment TTS events meeting confirmed, probable, or possible PRAC requested definition, 8 were in the Ad26.COV2.S group, 10 in the Placebo group, and 3 in the cross-vaccinated group, in which participants in the initially randomized Placebo group received Ad26.COV2.S at unblinding/crossover or were enrolled into study at open-label phase (ie, received Ad26.COV2.S). Of these 8 events reported in 7 participants receiving Ad26.COV2.S, the time to onset of symptoms was between 21 and 148 days following last vaccination. One participant was SARS-CoV-2 positive. Of the 10 events reported in 6 participants in the Placebo group, the time to onset was between 12 and 124 days following last vaccination. None of these participants were SARS-CoV-2 positive. The 3 events reported in 2 participants after cross-vaccination had a time to onset of 90 to 94 days following crossover vaccination. None of the participants were SARS-CoV-2 positive.

Upon request, details were provided:

In study COV1002: 1 participant in the Ad26.COV2.S group experienced a TTS 123 days post dose 2 and using PRAC criteria, was assessed as possible TTS.

In study COV3001: In the Ad26.COV2.S group, 8 AEs were reported for 7 participants. Out of those, 1

was assessed as confirmed (post dose 1) and 4 were assessed possible TTS (post dose 1 Ad26.COV2.S). In the placebo group, 8 AEs were reported for 6 participants. Out of those, 5 were assessed as possible TTS (post dose 1 of placebo). In the open-label cross-over group, 5 AEs were reported for 4 participants. Out of those, 3 were assessed as possible TTS (post dose 1 of open-label cross-over vaccination).

In study COV3009: In the Ad26.COV2.S group, 2 AEs were reported for 2 participants and were assessed as possible TTS. Both events occurred during the open-label phase of the study. In the placebo group, 6 AEs were reported for 3 participants. Out of those, 5 were assessed as possible. No event of TTS has been reported for the open-label cross-over vaccination.

Therefore, across all submitted clinical studies, only 2 events happened after two vaccinations with Ad26.COV2.S vaccine, both cases were assessed as "possible TTS" according to PRAC definition, but none of the cases was considered as causally associated with study vaccination by investigator (in particular because of the too long time-to-onset):

- One case happened in study COV1002 in Japan. This was a participant of 70-79 years old that reported an acute myocardial infarction 123 days after the booster dose (second dose) of Ad26.COV2.S $1x10^{11}$ vp. Platelet count at time of the event was $11.9x10^{4}$. AntiPF4 testing was performed during the study at sample collection timepoints pre and post vaccination, results are considered negative. Anti PF4 testing was not performed at the time of the event. The event had a fatal outcome.
- The other case was reported in study COV3009: a fatal event of myocardial infarction was reported for 1 participant in the Ad26.COV2.S 5×10^{10} vp group 118 days post-vaccination 2. Non serious thrombocytopenia was reported (60-69 year-old subject).

Currently the booster dose (second dose) of COVID-19 vaccine Janssen is approved only in the US. Based on the review of the CDC website on 05 December 2021, an estimated 669,631 doses of COVID-19 vaccine Janssen have been identified to have been administered as a booster dose (second dose) in the US, and 591,878 individuals have received COVID-19 vaccine Janssen for both primary vaccination and booster dose (second dose). No cases of TTS after the booster dose (second dose) of the COVID-19 vaccine Janssen vaccine have been reported in the post-marketing data.

Finally, to specifically address the potential effect of a booster dose (second dose) versus primary vaccine, the MAH has provided a comparison of acute phase proteins after the first, second and third dose in a non-clinical repeat dose toxicity study, driven by the hypothesis that the level of innate immune responses might be a predisposing factor for TTS. Fibrinogen and C-reactive protein appeared as largely similar after any dose.

Based on EEA exposure data for Vaxzevria, the estimated incidence rate of TTS is 12.8 per million following the first dose and 0.6 per million following the second dose (Article 5(3) Assessment report; EMA/530434/2021).

Ref:https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-final-assessment-report_en.pdf

Similarly, lower rate is also estimated from international data e.g. in UK 15.2 vs 2.0 per million doses, respectively for the first and second doses (MHRA).

Therefore, although the submitted data are limited with the booster dose (second dose) of COVID-19 vaccine Janssen, overall data (non-clinical, clinical, post-marketing data in US and Vaxzevria data) do not suggest an increase in frequency of TTS after the administration of a booster dose of vaccination compared to a single one.

In conclusion, the reactogenicity of the homologous booster dose (second dose) of Ad26.COV2.S 5×10^{10} vp (at least after 2-month after the 1st one) is consistent with the reactogenicity reported after administration of the first dose. No new unexpected safety concerns have been observed after the booster dose (second dose). Two possible cases of TTS were observed after a COVID-19 vaccine Janssen booster dose (second dose) (1 with 5×10^{10} vp dose, the other with 1×10^{11} vp dose, both fatal, none considered as causality associated with study vaccine). However, after the 2nd dose, the submitted data are limited in terms of the duration of follow up and number of vaccines included in the studies which does not allow any firm conclusions regarding the occurrence of uncommon or very rare AEs/SAEs and AEIs/AESIs (<1/10000) after the 2nd dose (such as TTS, GBS and CLS). Moreover, the number of patients with vaccination interval > 2 months is extremely low (unblinded data available for only 147 vaccinees with 2 doses of Ad26.COV2.S 5×10^{10} vp).

Following the COVID-19 Vaccine Janssen heterologous booster (after an approved mRNA COVID-19 vaccine regimen: 2 doses Spikevax or Comirnaty), the solicited adverse reaction profile was similar to that following a COVID-19 Vaccine Janssen primary vaccination or homologous booster dose. However, because of the very limited number of subjects in each group (±50), conclusion should not be considered as final.

The safety profile of COVID-19 Vaccine Janssen will continue to be closely monitored.

6. Real World Data and Vaccine Effectiveness

Introduction

At time of initial conditional MA, vaccine efficacy was 66.9% (Adjusted 95% CI: 59.03; 73.40) over a median follow-up time of 58.0 days for the prevention of symptomatic 'moderate to severe/critical' COVID-19 with an onset beyond Day 14, and 66.1% (Adjusted 95% CI: 55.01; 74.80) over the same period with an onset beyond Day 28, in seronegative adults ≥18 years who received one dose of $5x10^{10}$ vp, vaccine. For Severe COVID-19, VE was 76.7% (Adjusted 95% CI: 54.56; 89.0) with an onset beyond Day 14 and 85.4% (Adjusted 95% CI: 54.15; 96.9) with an onset beyond Day 28 over a median follow up of 58 days, in SARS-COV-2 seronegative subjects. Of the 14 vs. 60 severe cases with onset at least 14 days after vaccination in the Ad26.COV2.S group vs. placebo group, 2 vs. 6 were hospitalised. Subgroup analyses of the primary efficacy endpoint showed 82.4% [95% CI: 63.90; 92.38] efficacy in people ≥65 years, compared to 64.2% [95% CI: 55.26; 71.61] in participants 18-64 yoa with an onset beyond Day 14. For an onset beyond Day 28, VE was 74.0% [95% CI: 34.40; 91.35] and 65.1% [95% CI: 52.91; 74.45] in both age groups, respectively.

Vaccine efficacy analysis was evaluated in different countries: Brazil; South Africa; and the United States. Lower vaccine efficacy against COVID-19 was noted in 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) compared to the other regions. However for severe COVID-19, VE was consistently high, including in South Africa with onset at least 14 days after vaccination (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 in all countries.

Of all sequenced samples, in the United States, 96.4% of strains were identified as the Wuhan-H1 variant D614G; in South Africa, 94.5% of strains were identified as the 20H/501Y.V2 variant (B.1.351 lineage); in Brazil, 69.4% of strains were identified to be a variant of the P.2 lineage and 30.6% of strains were identified as the Wuhan-H1 variant 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.

Since the conditional MA in EU and EUA in the US, the Ad26.COV2.S vaccine has been used in national vaccination campaigns. In Europe, the vaccine has been distributed to 28 countries starting in calendar week 15 of 2021. The vaccine was never used in Finland, Liechtenstein and Sweden.

At this moment, real-world evidence (RWE) data is available from a Company-sponsored study in the US (VAC31518COV4002), a collaborative study in South-Africa (Sisonke) and several published RWE studies from the US and EU. A Company-sponsored study in the EU (VAC31518COV4004) is also ongoing, but no data are currently available.

COV4002

COV4002 is a company-sponsored observational longitudinal post-authorization case-control study in the US to assess effectiveness of a single dose of COVID-19 vaccine Janssen ($5x10^{10}$ vp), with onset 14 days after vaccination, in adults ≥18 years of age. This study is based on open-source medical claims data available in the Health Verity database of approximately 2.1 million individuals (422.034 vaccinated; 1.645.397 matched unvaccinated). Interim results are available up to 183 days (approximately 6 months) after vaccination, with a median follow up time of 129 days (approximately 4,5 months). Participants vaccinated with COVID-19 vaccine Janssen were matched to unvaccinated participants based on the same location (3-digit ZIP), age within 4 years, sex, and general health status captured in a comorbidity score. The co-primary objectives of the study are (1) to estimate the effectiveness of COVID-19 vaccine Janssen in preventing any asymptomatic or symptomatic COVID-19 and (2) to estimate the effectiveness of COVID-19 vaccine Janssen in preventing any COVID-19 related hospitalization (with diagnosis of COVID-19 or a recorded infection within 21 days before admission)

A limitation of this study is that a significant proportion of individuals in the 'unvaccinated group' may in fact be vaccinated but not recorded as vaccinated in the database due to the absence of an insurance claim. Vaccine effectiveness (VE) calculations have been corrected for this by assuming 40% under-reporting, calculated based on considering vaccination rates in the US reported by CDC and vaccination rates in the Health Verity database. However, the rate of under-reporting is an estimate and remains to be interpreted cautiously.

Corrected VE for any observed COVID-19 is 76% (95% CI:75 - 77) and slightly higher, 81% (95% CI: 78 - 82), for COVID-19 related hospitalization. Corrected VE is higher in younger individuals (18-64 yoa) compared to elderly (≥65 yoa), both for any COVID-19 (<65yoa: 78% (95% CI: 77 - 79); ≥65yoa: 72% (95% CI: 70 - 74)) and COVID-19 related hospitalization (<65 yoa: 85% (95% CI: 83-87); ≥65 yoa: 74% (95% CI: 70-77)). High protection against any SARS-CoV-2 infection as observed in this study is not in line with most other studies. Immunocompromised individuals have lower VE for observed COVID-19 (64%; 59 - 68) compared to non-immunocompromised individuals (77%; 95% CI: 76 - 78). Similarly, VE for Covid-19 related hospitalization was lower in immunocompromised individuals (67%; 95% CI: 57 - 74) than in non-immunocompromised individuals (82%; 95% CI: 80 - 83).

COVID-19 variant sequence data is not available, but a separate analysis of VE was done on data from the 4 states with a high incidence of the Delta variant from June to August 2021, which are Florida (72%), Louisiana (74%), Arkansas (91%) and Missouri (96%). In these states, VE during the Delta period was 74% (95% CI: 71-77) for any COVID-19 and 81% (95% CI: 75-86) for COVID-19 related hospitalization. During the entire period of the study from March to July, VE in these states was similar, respectively, 75% (95% CI: 72-78) and 80% (95% CI: 75-85). These results provide evidence that COVID-19 vaccine Janssen provides similar protection against the Delta variant compared to other circulating variants.

When evaluating VE over time, starting 14 days after vaccination, data indicates that protection against any COVID-19 remains sustained up to 183 days (approximately 6 months), with median follow-up of 129 days (approximately 4.5 months). For COVID-19 related hospitalization, VE remains sustained until

at 130 days (approximately 4.5 months) after vaccination (These data indicate there is no waning of VE during the limited follow-up period in the study. Similar analysis over a longer period will be needed to inform on the long-term protection after one dose of the vaccine.

In addition, VE was analyzed by month from March to August 2021 The data indicates that VE was stable during those months, both for COVID-19 and COVID-19 related hospitalization. In the 4 states with high incidence of the Delta variant from June to August 2021, there is a trend for a small reduction in VE against any COVID-19 in the months July and August, although not significant. For COVID-19 related hospitalizations, VE remains similar as before in these states during the high Delta incidence period. These data indicate that one dose of COVID-19 vaccine Janssen provides overall similar protection against COVID-19 caused by the Delta variant compared to other circulating variants in the US.

Sisonke study (COV3012)

The Sisonke study is a collaboration between the National Department of Health, South African Medical Research Council, Desmond Tutu Health Foundation, CAPRISA and Janssen. In this open-label implementation study, 477,234 Health Care workers in South Africa ≥18 years of age have been vaccinated with one dose of COVID-19 vaccine Janssen between February and May 2021. This period of the pandemic was first dominated by the Beta variant and then followed by the Delta variant. The objective of this study was to determine VE against hospitalization, ICU admission and death ascertained 28 days or more post vaccination, assessed up to 17 July 2021. Nested sub-cohorts (A and B) from 2 national medical scheme administrators / managed care organizations comparing unvaccinated population counterparts matched for COVID-19 risk, were evaluated to assess VE using a matched retrospective cohort design. To validate VE, comparison of HCWs with matched unvaccinated HCWs in a nested sub-cohort using a provincial health service data system was also performed.

VE derived from the A and B datasets comprising 215,813 HCWs was 83% (95% CI 75-89) to prevent COVID-19 deaths, 75% (95% CI 69-82) to prevent hospital admissions requiring critical or intensive care, and 67% (95% CI 62-71) to prevent COVID-19 related hospitalizations. This data confirms higher effectiveness for more serious outcomes. The MAH concludes also that VE was maintained in older HCWs and those with comorbidities including HIV infection, although no data was provided. The age distribution of participants in the trial is not provided, but as the healthcare force in South Africa are predominantly middle aged females, males and elderly are expected to be underrepresented in this study.

VE remained consistent throughout the Beta and the Delta dominant phases of the study. However, low number of events occurred during the Beta period, while the majority of cases occurred during the Delta period. VE estimates may thus be considered indicative for protection against the Delta variant. Based on these data, one dose of the COVID-19 Janssen vaccine shows to be protective against the Delta variant and overall to be in line with efficacy in the pivotal trial.

The follow-up period after vaccination is limited and longer term data are needed to evaluate if VE is sustained over time.

Real-world effectiveness publications

Real-world effectiveness (RWE) studies investigating VE of COVID-19 vaccine Janssen to prevent COVID-19, COVID-19 related hospitalization, ICU admission or death have been published recently. Studies are diverse as different study-designs are used and data emerges from different geographical regions; different populations; in the presence of multiple variants; and administration of vaccines according to local vaccination policies. Some studies are only assessing COVID-19 vaccine Janssen, while other studies compare VE between all authorized vaccines.

The majority of RWE studies published to date for COVID-19 vaccine Janssen have been conducted in the US and there is one EU study (The Netherlands). All data was obtained in the period from January to August 2021, when the Alpha and Delta variant were the predominant variants circulating.

VE against any COVID-19 was described by Corchado-Garcia et al., Sharma at al. and Cohn at al. Several other studies assessed VE against more severe COVID-19 (including Severe COVID-19, COVID-19 related hospitalization, COVID-19 related ICU admission and COVID-19 related death). Part of these analyses were performed before the Delta variant became dominant (Moline et al., Thompson et al., and Self et al.), while two studies in the US (Grannis et al. and Cohn et al.) and one in the Netherlands (De Gier et al.) report VE during the Delta period.

Corchado-Garcia et al. performed a multi-state study in the US (majority of participants form Minnesota and Wisconsin). Health records were retrieved from the Mayo Clinic Health System. More than 90% of population is Caucasian and approximately 54% are female. In this retrospective case-control study 2.195 vaccinated and 21.950 unvaccinated matched control individuals ≥18 years of age who underwent PCR testing for suspected SARS-CoV-2 infection were included between 27 February and 14 April 2021. The follow-up period after vaccination was very limited (maximum 48 days; median not provided). VE in preventing SARS-CoV-2 infection with onset at least 14 days after vaccination was 76.7% (96% CI: 30.3% - 95.3%). Confidence intervals are large due to a small number of PCR positive cases (3 out of 1.779 in vaccinated group; 128 out of 17.744 in control group). There were insufficient numbers of COVID-19 related hospitalizations, intensive care unit (ICU) admissions and deaths to assess the effect of vaccination on COVID-19 severity. The circulating variants in the concerned states during the study-period are not discussed, but during this period, the Alpha variant was dominant.

Sharma at al. performed a retrospective cohort-study of vaccine breakthrough infections in vaccinated adults ≥18 years of age from the US Veterans Health Administration database from 01 January through 31 August 2021. During this period, the Alpha and Delta variant were mainly circulating. The majority of the population are elderly males (median age: 70 years (interquartile range: 58-76 years)) and 227.570 individuals were vaccinated with COVID-19 vaccine Janssen. The objective of this study was to determine the frequency of breakthrough infections with an onset at least 14 days after full vaccination with any of the available vaccines (COVID-19 vaccine Janssen, Comirnaty or Spikevax). However, no VE data for COVID-19 vaccine Janssen is provided, only data on the comparison of breakthrough cases between different the different vaccines. These analyses show that compared to COVID-19 vaccine Janssen, vaccination with Comirnaty or Spikevax results in lower occurrence of documented SARS-CoV-2 infection up to 200 days after full vaccination (aHR 0.54, 95% CI 0.51-0.58; aHR 0.36; 95% CI 0.33-0.38; respectively). Similarly, effectiveness against COVID-19 related hospitalization was also lower for COVID-19 vaccine Janssen compared to mRNA vaccines (aHR 0.56, 95% CI 0.47-0.66; aHR 0.30; 0.25-0.35; respectively). The authors conclude there is a strong relationship between the proportion of the Delta variant and occurrence of breakthrough infections.

The COVID-19 Associated Hospitalization Surveillance Network (COVID-NET) reported on the effectiveness of COVID-19 vaccines in preventing hospitalization among adults aged ≥65 years in 13 US states from 1 February to 30 April 2021, which is during the Alpha dominant period (Moline 2021). Of note, the COVID-19 vaccine Janssen was only used since 15 March 2021 and therefore, the follow-up period is very short. COVID-19 vaccination status was collected from State Immunization Information Systems (IIS). Poisson regression analysis was used to compare COVID-19 case counts (hospitalizations) by vaccination status. The proportion of hospitalization in the population vaccinated was compared to the unvaccinated population. Potential confounders were accounted for but the analysis did not adjust for all confounders such as chronic underlying conditions. In total 7.280 cases were included, of which only 394 were fully vaccinated (at least 14 days since last vaccination) with one of the available COVID-19 vaccines. The sample size of fully vaccinated individuals with the COVID-19 vaccine Janssen was very

limited (16 of 65-74 yoa; 8 ≥75 yoa). VE of this vaccine to prevent COVID-19 associated hospitalizations was similar in both age groups; 84% (95%CI: 64 - 93) for adults aged 65-74 years and 85% (95% CI: 72- 92) for adults aged ≥75 years.

Thompson et al. assessed VE of all available COVID-19 vaccines in ambulatory and inpatient care settings in adults of ≥ 50 years of age by a test negative case-control study. Data was generated through the VISION Network which is a collaboration between the Center for Disease Control and 7 United States Healthcare systems and research centers. VE with onset at least 14 days after vaccination was assessed for all available COVID-19 vaccines against hospitalization and ICU admission between 01 January and 22 June 2021, when the Alpha-variant was predominantly circulating. For COVID-19 vaccine Janssen, VE is 68% (95% CI: 50 - 79) against laboratory confirmed SARS-COV-2 infection leading to hospitalization and 73% (95% CI: 59 - 82) against infection leading to an emergency department or urgent care clinic visit, represented by 707 and 456 vaccinated individuals, respectively. With a median of 42 to 53 days from full vaccination to index date (similar for all COVID-19 vaccines in the study), the follow-up after vaccination is relatively short.

Self et al. published a prospective case-control study to determine VE in preventing COVID-19 hospitalizations with onset at least 14 days after full vaccination in adults ≥ 18 years old (median age: 61 years (57-77)) without immunocompromising conditions in the US. The analysis used data of 21 hospitals within the Influenza and Other Viruses in the Acutely Ill (IVY) Network between 11 March and 15 August 2021, covering the Alpha and Delta dominant period. VE of COVID-19 vaccine Janssen for prevention of COVID-19 related hospitalization was 71% (95% CI: 56 - 81). The number of participants vaccinated with COVID-19 vaccine Janssen was limited (n=113) in this study, resulting in large CI. In addition, due to the limited sample size, VE could not be stratified by time.

The VISION network (Grannis et al.) investigated VE in adults against COVID-19 associated emergency department or urgent care clinic encounters and hospitalizations with onset at least 14 days after full vaccination within 9 US states from June through August 2021 in adults ≥ 18 year of age by using a test negative case-control design. As during the study period the Delta variant was predominantly circulating (>50% of sequenced isolates), the data gives some indication for VE against this variant. VE of COVID-19 vaccine Janssen for prevention of COVID-19 related hospitalization was 60% (95% CI: 31-77) and 65% (95% CI: 56 – 72) against ICU admission. The number of participants fully vaccinated with COVID-19 vaccine Janssen was limited (n=458) in this study, resulting in large CI. The median interval from vaccination to the hospital or ICU admission was 94 days. No VE analysis stratified by time was done.

A study of COVID-19 VE against hospitalizations and ICU admission in the Netherlands was carried out from 04 April through 29 August 2021 using data from the national COVID-19 vaccination register (CIMS) and the national register of COVID-19 hospitalizations (NICE) (de Gier et al.). During the study, there was an Alpha predominant (95% prevalence; 04 April to 29 May 2021) and a Delta predominant period (99.9% prevalence; 4 July to 29 August 2021). All subjects vaccinated with COVID-19 vaccine Janssen were below 70 years old as for the elderly other vaccines were used. The objectives are to estimate VE against COVID-19 hospitalization and ICU admissions per period (Alpha and Delta), per vaccine and per time since vaccination. However, as there was only a small number of fully vaccinated hospitalizations during the Alpha period, VE by vaccine type has only been calculated for the Delta period. During this period, VE against COVID-19 related hospitalization was 91% (95% CI: 88-94) and VE against COVID-19 related ICU admission was 94% (95% CI: 88 - 98), when considering onset at least 28 days after vaccination. VE was similar in all age groups and no waning was observed up to 20 weeks after vaccination, overall for all available COVID-19 vaccines.

Cohn et al. assessed VE against COVID-19 infection and death in US Veterans. This study was published after the submission of RWE data by the MAH and was therefore not included in the Real-world evidence summary report of 06 October 2021. A test-negative case control study was performed on data of

780,225 veterans in the US Veterans Health Administration database, of which 35,662 were vaccinated with COVID-19 vaccine Janssen. The same database was used in the study of Sharma at al. (discussed above). The analysis was performed on data retrieved in the period from 1 February 2021 to 1 October 2021, covering the Delta-predominant period starting in July 2021. The majority of the population in this analysis are males (89%) with an age >50 (25% of <50 yoa; 38% of 50-64 yoa; 36% of ≥65 yoa) and white (70%). Most Veterans vaccinated with COVID-19 vaccine Janssen received the vaccine between March and June. The objective of the study was to assess VE against COVID-19 infection or COVID-19 related death with onset at least 15 days after vaccination. VE estimates were adjusted for age, race, ethnicity, sex, and comorbidity score. During the study period, VE against infection declined for all vaccine types, with the greatest decline for COVID-19 vaccine Janssen. In March, VE for COVID-19 vaccine Janssen was 86.4% (95% CI: 85.2% - 87.6%), while by September, VE was declined to 13.1% (95% CI: 9.2% - 16.8%). The authors describe that this was similar across age groups and time since vaccination. In contrast to VE against infection, VE against death was overall better sustained during the delta period, especially in younger individuals < 65 years old showing VE of 81.5% (95% CI: 70.7% - 88.4%) while in individuals ≥ 65 years VE was 52.2% (95% CI: 37.2% - 63.6%). To conclude, these results indicate that COVID-19 vaccine Janssen proves less protection against infection during the Delta period. In this period, vaccination still provides protection against COVID-19 related death, although, especially in elderly the benefit is reduced.

Limitations

RWE data should be interpretated with caution as there are several limitations and potential biases that could have an important impact on the results.

First of all, different study designs and methodologies each have their own strengths and limitations for estimating VE. Also the databases that are used as source of vaccination status and SARS-CoV-2 infection status can introduce bias, as there is a risk of misclassification or under-recording of vaccinations, as well as SARS-CoV-2 infections, due to several reasons (including health care claims data where reimbursement is not collected through insurance claims in the US; privacy-related issues). In some studies, VE estimates have been corrected for expected under-recording, however as the exact misclassification rate is difficult to predict precisely, the impact on the results remains uncertain and may lead to bias.

Furthermore, differences between study populations, including underlying comorbidities and other risk factors; age; demographics; and socioeconomic factors, make it also difficult to directly compare point estimates for VE across studies.

Methodological differences in case definitions used in different studies could impact VE estimates and is a limitation to make comparisons between studies.

Besides limitations inherent to RWE studies, a limitation of the currently available RWE data for the COVID-19 vaccine Janssen is the short follow-up period and in addition, the lack of analyses stratified for different follow-up periods after vaccination. As a consequence, currently available data is insufficient to make any conclusions on potential waning of effectiveness over time against COVID-19, COVID-19 related hospitalization or COVID-19 related ICU admission.

In addition, the appearance of new variants will be a remaining challenge to deal with when analyzing long-term data as in many cases, the effect of waning and appearance of variants are difficult to disentangle form each other. As sequencing data of SARS-CoV-2 variants are usually lacking in RWE studies, an indication of VE against a specific variant can only be estimated when a variant is known to be predominant at a certain time and location.

Most studies assessed VE against COVID-19 with onset at least 14 days after vaccination, while in some studies a period of 28 days was considered. Although analysis of the pivotal trial at time of marketing authorization suggested that the onset of protection is around Day 14 post-vaccination, it was also shown that onset of protection occurred later, around Day 28, in South Africa. It was hypothesized that immune responses of higher magnitude are needed for protection against the main variant circulating at that time in South Africa (20H/501Y.V2 variant). This should be taken into

consideration when interpreting data of VE against the Delta variant, as a similar hypothesis could apply as well.

Of note, many of the available publications are pre-prints and not yet peer-reviewed, which should therefore be interpreted with caution.

Finally, a limitation of all real-world effectiveness studies that are published is the limited use of the COVID-19 vaccine Janssen in EU and the US compared to the mRNA vaccines, resulting in relatively small sample sizes. In addition, the later rollout compared to the mRNA vaccines has as implication that many elderly were already vaccinated with an mRNA vaccine. The company-sponsored study in the US (VAC31518COV4002) and the collaborative study (Sisonke) in South-Africa are therefore considered most relevant and informative. The company-sponsored European study (VAC31518COV4004) is expected to provide relevant data on RWE in EU.

Conclusion

Available post-marketing RWE data obtained during the period before the Delta-variant became dominant and when the Alpha variant was mainly circulating, indicate that vaccine effectiveness after one dose of COVID-19 vaccine Janssen is overall in line with vaccine efficacy in the pivotal trial COV3001 at time of conditional MA.

During the Delta-predominant period, data from several studies (mainly from the US and the NL) indicate that vaccination with COVID-19 vaccine Janssen overall results in sustained protection against more severe COVID-19 (including hospitalization, ICU admission and death). For any SARS-COV-2 infection or any symptomatic COVID-19, data are currently inconclusive. While the company-sponsored study COV4002 in the US shows good protection against any SARS-COV-2 infection, very low VE was observed in a study with US Veterans, which is more in line with the trial data. In addition, many limitations related to RWE data are certainly contributing to differences between study results, which should be considered cautiously.

Available RWE data, is currently insufficient to conclude about the duration of protection and potential waning of effectiveness after one dose of COVID-19 vaccine Janssen as long-term VE data is currently lacking.

The MAH is planning to gather RW evidence on both, homologous and heterologous booster effectiveness. The studies **VAC31518COV4002 and VAC31518COV4004** are being amended to include analysis of effectiveness of additional homologous or heterologous booster vaccination. The open-label phase of **COV3001** include as objectives to estimate effectiveness of additional homologous or heterologous vaccine boosting. A new ongoing study sponsored by the he South African Medical Research Council (**Sisonke boost**) is enrolling Sisonke participants to administer a homologous boost of Ad26.COV2.S and assess safety and effectiveness of booster vaccination. Additional collaborative studies assessing real-world (heterologous and homologous) boosting vaccine effectiveness are currently in discussion with collaborators.

Table 19. Summary Real-world effectiveness studies

Study	countries	data source	Study design	population	Sample size	Period	Follow-up	objectives	Main variants
Janssen-Sponsored									
COV4002	US	HealthVerity database	Cohort	Adults ≥ 18 yoa	2.1 million: 422.034 vaccinated; 1.645.397 matched controls	01 Mar 2021 – 31 Aug 2021 Delta: 01 Jun 2021 – 17 Aug 2021	180 days (max) Median follow-up time: 129 days	Co-primary: to estimate VE in preventing (1) any (a)symptomatic COVID-19; (2) to any COVID-19 related hospitalization with onset 14 days after vaccination	Alpha Delta
Collaborative									
Sisonke COV3012 (Bekker 2021)	South-Afrika	National Institute for Communicable Diseases (NICD) in the COVID-19 notifiable medical conditions sentinel surveillance (NMCSS) system.	Cohort	Health Care workers in South Africa ≥18 yoa	477,234 HCWs vaccinated VE calculated based on data of 215,813 HCW	Feb 2021 – Jul 2021	140 days (max)	VE against hospitalization, ICU admission and death ascertained 28 days or more post vaccination.	Beta Delta
Literature									
Corchado-Garcia 2021	US (mainly Minnesota and Wisconsin)	Multi-state Mayo Clinic Health System's EHRs;	Cohort	Adults aged ≥18 years	2,195 vaccinated; 21.950 unvaccinated	27 Feb 2021 - 14 Apr 2021	48 days (max)	VE with onset at least 14 days after vaccination	Alpha

Study	countries	data source	Study design	population	Sample size	Period	Follow-up	objectives	Main variants
Moline 2021	US (13 states)	COVID-19-Associated Hospitalization Surveillance Network (COVID-NET)	proportion of COVID-19 hospitalized vs population vaccine status	Adults aged ≥65 years	7,280 (total for Pfizer-BioNTech, Moderna and Janssen) 5,451 (75%) were unvaccinated, 867 (12%) were partially vaccinated, and 394 (5%) were fully vaccinated	Feb 2021 – Apr 2021	Not specified	VE with onset at least 14 days after vaccination	Alpha
Thompson 2021	US	VISION network	Test-negative case-control	Adults aged ≥ 50 yoa	707 fully vaccinated; 10.761 unvaccinated controls	01 Jan 2021 - 22 Jun 2021	Not specified	VE with onset at least 14 days after vaccination	Alpha
Grannis 2021	US	VISION network	Test-negative Case-control	Adults aged ≥ 18 yoa	458 fully vaccinated; 6960 unvaccinated controls	Jun 2021 – Aug 2021	94 days	VE with onset at least 14 days after vaccination	Delta

Study	countries	data source	Study design	population	Sample size	Period	Follow-up	objectives	Main variants
Self 2021	US	21 hospitals within the Influenza and Other Viruses in the Acutely Ill (IVY)	Case-control	Adults aged ≥ 18 yoa median age: 61 (57-77)	113 vaccinated 37/1500 vaccinated case-patients and 76/975 vaccinated control-patients	Mar 2021 – Aug 2021	29 weeks (max; for all vaccines)	VE with onset at least 14 days after vaccination	Alpha Delta
Sharma 2021	US	Veterans Health Administration (VHA)	cohort	Adults aged ≥ 18 yoa median age: 70 (58-76)	227.570	01 Jan 2021 - 31 Aug 2021	5 months (max)	COVID-19 incidence with onset at least 14 days after vaccination	Alpha Delta
de Gier 2021	The Netherlands	hospitalized persons with positive SARS-CoV-2 test or CT-confrimed COVID-19 registered in NICE COVID-19 registry	cohort study with a test negative design	15 - 69 yoa	Not specified	04 Apr 2021 - 29 Aug 2021	Not specified	COVID-19 incidence with onset at least 14 and 28 days after vaccination	Alpha Delta
Cohn 2021 *Not included in RWE summary report of 06Oct2021*	US	Veterans Health Administration	cohort	Veterans	35, 662	01 Feb 2021 – 01 Oct 2021	5 months	VE with onset at least 15 days after vaccination	Alpha Delta

Table 20. Summary Real-world effectiveness data

Study	Country	Vaccine effectiveness against COVID-19 % (95% CI)					VE against COVID-19 caused by Delta % (95% CI)				
		Any	Severe	Hospital.	ICU	Death	Any	Symptomatic	Hospital.	ICU	Death
Janssen-Sponsored											
COV4002	US	**76** (75-77) <65yoa: **78** (77-79) ≥65yoa: **72** (70-74)	/	**81** (78-82) <65yoa: **85** (83,87) ≥65yoa: **74** (70,77)	/	/	**74** (71-77)	/	**81** (75-86)	/	/
Collaborative											
Sisonke COV3012 (Bekker 2021)	South-Afrika	/		**67** (62-71)	**75** (69-82)	**83** (75-89)	/	/	/	/	/
Literature											
Corchado-Garcia 2021	US (mainly Minnesota and Wisconsin)	**76.7** (30.3; 95.3)	/	/	/	/	/	/	/	/	/
Moline 2021	US (13 states)	/	/	65-74 yoa: **84** (64-93) ≥75yoa: **85** (72-92)	/	/	/	/	/	/	/

Thompson 2021	US	/	/	**68** (50;79)	**73** (59;82)	/	/	/	/	/	/
Grannis 2021	US	/	/	/	/	/	/	/	**60** (31-77)	**65** (56-72)	/
Self 2021	US	/	/	**71** (56-81)	/	/	/	/	/	/	/
Sharma 2021	US	Vaccine breakthrough events most frequent for COVID-19 vaccine Janssen	Vaccine breakthrough events most frequent for COVID-19 vaccine Janssen	/	/	/	/	/	/	/	/
de Gier 2021	The Netherlands	/	/	/	/	/	/	/	14 days: **82** (56-93) 28 days: **91** (88-94)	14 days: **83** (-22-98) 28 days: **94** (88-98)	/
Cohn 2021 *Not included in RWE summary report of 06Oct2021*	US	Mar: **86.4** (85.2 – 87.6)	/	/	/	/	/	Sep: **13.1** (9.2-16.8)	/	/	<65 yoa: **73.0** (52.0 – 84.8) ≥65 yoa: **52.2** (37.2 – 63.6)

7. Changes to the Product Information

As a result of this variation, sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are being updated to introduce a booster dose (second dose) in individuals aged 18 years and older. The Package Leaflet (PL) is updated accordingly. Please refer to Attachment 1.

8. Overall conclusion and impact on the benefit/risk balance

Requested Variation

COVID-19 Vaccine Janssen (Ad26.COV2.S) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The approved posology is a single dose of $5x10^{10}$ vp in 0.5 mL, to be administered intramuscularly.

In the current variation, the MAH is seeking a posology for homologous booster immunization at least 2 months after primary vaccination in individuals 18 years of age or older and the use of Ad26.COV2.S for heterologous booster immunization following completion of primary vaccination with an approved mRNA COVID-19 vaccine.

Need for a booster vaccination

The available clinical data from study **COV3001** indicate that no drop of efficacy against severe COVID-19 was observed at least up to 6 months following a single dose of Ad26.COV2.S. Efficacy was maintained at 73% (95% CI: 63.9; 80.5), despite the emergence of diverse variants. At the primary analysis, the efficacy against severe disease was 77% (95% CI: 54.6; 89.1). There was little variability in terms of efficacy across the variants for severe COVID-19 (compared to symptomatic COVID-19), with efficacy point estimates maintained over 60% for the variants for which sufficient data were available (Beta, Gamma, Mu). Efficacy was higher for the reference strain (around 90%).

Efficacy against symptomatic COVID-19 was poor over the 4-6 months post-vaccination period. The estimates were 67% (95% CI: 59.0; 73.4) and 56% (95% CI: 51.3; 60.8) respectively in the primary (median follow up (FU) 2 months) and final (median FU 4 months) analyses. A drop of efficacy was observed rapidly (a few weeks following vaccination), in parallel with the progressive disappearance of the reference strain and emergence of several variants. Although it is not possible to firmly disentangle the role of waning of protective immunity from the role of variants, the observed drop is considered more likely mainly due to emergence of variants for which there was a decreased efficacy. The efficacy point estimates are good (approx. 70%) for the reference and the Alpha variant, as well as for the Zeta/P2 variant (approx. 65%). However, the efficacy point estimate was much lower for the Beta (approx. 40%), the Gamma/P.1 (approx. 35%) and the Mu (approx. 35%) variants. For the Lambda/C.37 efficacy point estimate was approx. 10%. The limited data for the Delta variant, also point to a signal of lack of efficacy (point estimate -6%, based on 11 vs 10 cases in the Ad26.COV2.S group vs the placebo group).

Available post-marketing **real world evidence (RWE)** data obtained during the period while the Alpha variant was the mainly one circulating and before the Delta-variant became dominant, indicate that the vaccine effectiveness after one dose of Ad26.COV2.S is overall in line with the efficacy data at time of initial conditional marketing authorisation (MA). During the Delta-predominant period, several studies (mainly from the US and the NL) indicate that protection is sustained against more severe COVID-19 (including hospitalization, ICU admission and death), while data are inconclusive for any SARS-COV-2 infection or any symptomatic COVID-19. The data is currently insufficient to conclude about the duration

of protection and potential waning of effectiveness after one dose of Ad26.COV2.S as long-term vaccine effectiveness (VE) data are currently lacking.

Neutralizing and binding antibody (Ab) levels evaluated in **clinical studies after a single dose of Ad26.COV2.S** appear to be sustained up to at least 6 months. There is no clear decrease of the antibody levels over time. A minor, and not systematic, trend for decreased Ab levels is observed at the later timepoints (6 or 8-9 months post-vaccination) when compared to earlier timepoints (1 or 2 months post-vaccination). This decrease was not considered significant, since 95% confidence intervals (CIs) always overlapped. Based on available clinical data, it is not possible to conclude if these observations suggest the start of a waning of humoral immune responses or are only due to variability inherent to the limited sample. It is not known if the Ab levels will decrease or will be maintained after 6-9 months post-vaccination with 1 single dose of Ad26.COV2.S, and if this will impact the clinical protection. Based on data of a few subjects, T cell responses appear to be sustained over time.

Based on very limited data, neutralizing capacity against the Delta and the Beta variants appear to be lower compared to the original strain and the Alpha strain.

Alternative approaches

Humoral immune responses after a homologous or heterologous boost with an mRNA vaccine, at least 12 weeks after primary vaccination, are investigated in the **Mix-and-Match study (DMID 21-0012)** conducted by NIH/NIAID (Atmar *et al.*). While antibody responses increase after both a homologous or heterologous boost, the data indicate that the homologous regimen with Ad26.COV2.S induces the lowest neutralizing and binding Ab responses. Humoral responses were much higher 14 days after boosting with an mRNA vaccine (Comirnaty or Spikevax). Due to the limited sample size, differences observed are only descriptive.

Main clinical studies

Results supporting the use of Ad26.COV2.S for homologous booster immunization at least 2 months after primary vaccination are from five ongoing studies, of which 3 Phase 1/2 studies evaluate the immunogenicity and safety of Ad26.COV2.S (**COV1001, COV1002 and COV2001**) and 2 large Phase 3 trials evaluate the efficacy, safety, and immunogenicity of Ad26.COV2.S in adults (**COV3001 and COV3009**).

Immunogenicity and safety data are the key data to support the variation. Results are from four studies for immunogenicity (COV1001, COV1002, COV2001, and COV3009), while the main safety data are from the double-blind phase of study COV3009.

Study results from the Phase 1/2 study DMID 21-0012, an ongoing heterologous platform boost study conducted by NIH/NIAID in the US (published in Atmar *et al.*) were also included to support the use of Ad26.COV2.S for heterologous booster immunization following completion of primary vaccination with an approved mRNA COVID-19 vaccine.

Supportive efficacy data are presented up to the end of the double-blind phase for COV3001 and COV3009. The trials assessed respectively a single- and a 2-dose schedule two months apart vs. placebo.

Favourable effects

Immunogenicity

A booster dose of Ad26.COV2.S, given at 2, 3 or 6 months post-primary vaccination, induces an increase in both neutralizing and binding Ab against the original strain and variants of concern (VOC), when compared to pre-boost values, both in young and older adults. GMTs increase, ranging from 1.5 to 4.4

fold for neutralizing antibodies (nAb) and from 2.5 to 5.8 fold for binding Ab, between pre-boost and 1 month post-boost.

Functional Ab against the original strain with a suggested role in viral clearance in vivo tend to increase post-dose 2.

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

Efficacy

The clinical trial COV3001 assessed a single dose of Ad26.COV2.S in multiple countries (US, several countries in Latin America, South Africa). There was a high diversity of variants amongst cases, without a dominant variant. Efficacy against moderate/severe COVID-19 (onset >14 days after vaccination) was 67% (95% CI: 59.0; 73.4) and 56% (95% CI: 51.3; 60.8) respectively over a 2 months and a 4 months median FU period. Efficacy against the Alpha variant was 70% (95% CI: 35.1; 87.6) over a 4 months FU period.

The clinical trial COV3009 assessed a 2-dose schedule given 56 days apart vs placebo in multiple countries (US, several countries in Europe and in Latin America, South Africa, Philippines). Alpha and Mu were the two dominant variants. Efficacy of two doses of Ad26.COV2.S administered two months apart was 75% (95% CI: 54.6; 87.3) against moderate/severe COVID-19 (onset >14 days post-dose 2) over a median FU period of 36 days. Efficacy against the Alpha variant was 94% (95% CI: 62.9; 99.9).

Comparison of data across clinical trials suggests that a booster dose (second dose) administered 2 months after the first might provide additional protection against symptomatic COVID-19 including for variants, but do not suggest a major added value.

Uncertainties and limitations related to favourable effects

There are a number of uncertainities and limitations related to immunogenicity and efficacy which are briefly listed here:

Immunogenicity

- There are no results from a dedicated booster study. The study COV2008, which evaluates the immunogenicity, reactogenicity and safety of Ad26.COV2.S administered as a booster, is ongoing.
- The humoral immune responses elicited by a booster dose was only investigated before immunogenicity started to wane.
- Results are from different studies, always with limited sample size, in particular for nAb.
- Most of the results are for the original Victoria strain. Limited data are available for the VOC. There are no Ab data for the Delta variant when the booster dose (second dose) is given at 2 months post-dose 1. Only limited data are available when the booster dose (second dose) is given with a 6 month-interval and several limitations have to be considered. First of all, data is generated by a developed (non-qualified) psVNA that seems to lack sensitivity. In addition, immune responses for these subjects do not follow the same kinetics up to 6 months post-dose 1 compared to other studies.
- nAb levels observed 1 month post-boost for the variants are lower than for the parental strain.
- A post-hoc non-inferiority analysis was performed on 17 subjects that received a boost 6 months after the primary vaccination. Since pre-boost Ab levels were not declined compared to 1 month post-dose 1, this analysis is not considered relevant.

- Data over a FU period of more than 1 month post-dose 2 are limited. A 2-fold decline of Ab titers is observed at 4-6 months post-dose 2 when the booster is given with a 2 or 3 month interval, while there is no decline in Ab titers post-dose 1. Whether Ab titers will continue to decline over time is not known. There are no long-term data when a boost is given 6 months post-dose 1.
- COV2001 is the only study that allows comparison of different time-interval (2 vs 3 months) between groups of the same age range. Data for the boost at 6 months post-primary vaccination are limited. Overall, data are too limited to conclude on the optimal time interval between doses.
- CMI data are very limited and from 1 study only.
- The potential impact of vaccine-induced anti-Ad26 immunity on immunogenicity remains unclear and should be further documented. This can have its importance if regular boosters are needed.
- Data of study DMID 21-0012 indicate the homologous regimen with Ad26.COV2.S induces the lowest Ab response, compared to heterologous boosting with an mRNA vaccine and to a homologous mRNA regimen.
- Results of study DMID 21-0012 also suggest that heterologous boosting with Ad26.COV2.S after primary vaccination with an mRNA vaccine induces lower Ab levels compared to homologous boosting with an mRNA vaccine after 14-days while after 1 month, neutralizing antibody titers are roughly similar between both regimens.
- There are no established immune correlate of protection, although it is recognized that Ab are associated with protection. The clinical relevance of these observations is not known.

Efficacy

- The efficacy of a booster was not studied as none of the trials was designed to assess superiority of the two-dose schedule over the single dose schedule, or to make any direct comparison between a two-dose and a single-dose schedule.
- Efficacy data are available for a single and for 2-dose schedule with 2 months interval from separate trials. Based on the available data, it is not possible to make robust conclusions on the efficacy of a booster dose.
- The efficacy point estimate was numerically higher in COV3009 assessing a 2-dose schedule compared to the point estimate in trial COV3001 assessing a single dose, but CIs widely overlap.
- There are limited data by SARS-CoV-2 variants for the two-dose schedule. The efficacy estimate against the Alpha variant is higher in COV3009 compared to the estimate in COV3001, but with widely overlapping CIs. Efficacy was not demonstrated for the Mu variant, and could not be estimated for other variants in COV3009, due to insufficient numbers. There are very limited data on the currently most relevant variant which is the Delta. In addition, spike sequence data were available for only 68% of the cases with an imbalance across arms, possibly leading to biases. Follow-up period varied across countries, variants distribution evolved over time and differed across countries, which could also lead to biases when estimating efficacy by variants.
- Beside the limitations associated with comparing data across trials, several important limitations have been identified in trial COV3009. Given the huge discrepancy between the FAS and the PP (approximately half of the subjects were excluded from the PP set), the analysis cannot be considered as resulting from a randomized comparison. Data from this trial raises some concern with respect to awareness of treatment allocation.
- The very short time of FU (36 days post-dose 2) also considerably limits the interpretation of the results of study COV3009.
- There are very limited data on severe cases and in elderly for the two dose schedule.
- All these issues raise concern on the robustness of the findings of COV3009, especially for the variants.
- Efficacy is lacking for asymptomatic cases, either after a single dose or after two doses of Ad26.COV2.S.

Unfavourable effects

The main safety data are from the double-blind phase of the phase 3 study COV3009: 8,655 subjects were vaccinated with 2 doses of Ad26.COV2.S 5×10^{10} vp with 56-day interval (FAS); the safety subset includes 1,559 participants in the Ad26.COV2.S group for dose 2. In the FAS, the overall median exposure time in the Ad26.COV2.S group was: 71d after the 1st vaccination and 38d after 2nd vaccination. Although limited, overall, the clinical data indicate that the reactogenicity of a second 5×10^{10} vp Ad26.COV2.S dose after 2 months is consistent with the reactogenicity observed after the first Ad26.COV2.S dose. Across all groups of participants who received 2 doses of Ad26.COV2.S at the 5×10^{10} vp or 1×10^{11} dose level with a 2- or 3-month interval, and for participants who received a primary dose of 5×10^{10} vp followed by antigen presentation with 1.25×10^{10} vp 6 months later, the reactogenicity profile is reassuring with similar or decreased reactogenicity after the 2nd dose compared to the 1st. A trend towards a decrease in the frequency and severity of solicited AEs with increasing age of participants was observed post-dose 1 and post-dose 2 Ad26.COV2.S administration (18-30 year-of-age vs. 31-45 vs. 46-55 vs. ≥65 years; or 18-59 vs. >60 years).

No new unexpected safety concerns have been observed after the 2nd dose. Two possible cases of TTS were observed after a Ad26.COV2.S booster dose (1 with 5×10^{10} vp dose, the other with $1x10^{11}$ vp dose, both fatal, none considered as causality associated with study vaccine). Overall, data (non-clinical, clinical, post-marketing data in US and Vaxzevria data) do not suggest an increase in frequency of TTS after the administration of a booster dose of vaccination compared to a single dose.

In study DMID 21-0012, following the COVID-19 Vaccine Janssen heterologous booster (vaccination with Ad26.COV2.S 5×10^{10} vp at least 12 weeks after primary vaccination with an approved mRNA COVID-19 vaccine regimen: Cominarty or Spikevax), the solicited adverse reaction profile was similar to that following a COVID-19 Vaccine Janssen primary vaccination or homologous booster dose (with Ad26.COV2.S 5×10^{10} vp).

Uncertainties and limitations related to unfavourable effects

For the homologous booster (2nd dose of COVID-19 vaccine Janssen), the submitted data are limited in terms of the duration of follow up and number of participants included in the studies which does not allow any firm conclusions regarding the occurrence of uncommon or very rare AEs/SAEs and AEIs/AESIs (<1/10000) after the 2nd dose (such as TTS, GBS and CLS). Moreover, the number of patients with a vaccination interval longer than 2 months is extremely low since unblinded data is available for only 147 vaccinees with 2 doses of Ad26.COV2.S 5×10^{10} vp.

With regards to te heterologous booster, the conclusion should not be considered final because of the very limited number of participants in each study group (±50 participants).
Therefore, given these uncertainties, appropriate routine risk minimization measures have been proposed in the product information.

Finally, additional safety data will be collected after the booster dose in the remit of the ongoing studies COV2008, COV3009 and DMID 21-0012.

Overall conclusion

At the moment, the need for booster vaccination with Ad26.COV2.S cannot be justified in terms of restoring immune response, given that following a single dose of Ad26.COV2.S, there is no clear evidence of waning of immunity up to 8-9 months. Efficacy against severe COVID-19 after a single dose of Ad26.COV2.S is sustained at a good level over a 6 months period for the reference strain and variants, which is supported by real-world effectiveness data. Nevertheless, lower neutralizing capacity

against some VOCs has been shown compared to the reference strain. Consistently, very low or lacking efficacy against symptomatic COVID-19 caused by certain variants is observed. This implies that a booster dose can be justified in terms of restoring protection that has been lost because of variants. There is a need to better protect individuals who received a single dose of Ad26.COV2.S.

Immunogenicity data show an increase in the humoral responses, including for variants, when a booster dose is administered 2, 3 or 6 months after the first dose. For the parental strain, the GMTs increases observed between pre-boost and 1 month post-boost range from 1.5 to 4.4 fold for nAb and from 2.5 to 5.8 fold for binding Ab. The data for the variants are very limited and, most of them, generated by using non-qualified assays. For the Delta variant, only limited data is available when the booster is administered with an interval of 6 months, while there is no data with a 2- or 3- month interval. Most of the data are available only for a short FU period post-dose 2 (i.e. 1 month). There are currently no data from a dedicated booster study. Although it is recognized that Ab levels are associated with protection, in the absence of an established immune correlate of protection, the clinical relevance of these observation is not known. CMI data are limited and do not suggest an increase in the CD4 and CD8 Th1 responses with a booster dose.

Overall, the available efficacy data at this stage are not sufficient to confirm that efficacy is increased with a booster dose. Evidence across the phase 3 trials suggest that a booster dose (second dose) administered at 2 months might increase the level of efficacy against symptomatic COVID-19, including for variants. Data suggest that the increment could be limited. However, due to several sources of uncertainty, no firm conclusion can be drawn on the clinical added value (and magnitude of) a booster dose of Ad26.COV2.S. No data are available for the Delta variant.

Based on the overall evidence (immunogenicity and efficacy), a benefit of administering a homologous booster dose of the Janssen COVID-19 vaccine after at least 2 months can reasonably be assumed, but this benefit is probably limited.

Current evidence suggest that an heterologous boosting with Ad26.COV2.S after primary vaccination with an mRNA vaccine induces lower Ab levels compared to homologous boosting with an mRNA vaccine after 14-days, while after 1 month, neutralizing antibody titers are roughly similar between both regimens. Data indicate the homologous regimen with Ad26.COV2.S induces the lowest Ab response compared to heterologous boosting with an mRNA vaccine and to a homologous mRNA regimen.

To conclude, there are many uncertainties on the benefit of administering a booster dose with Ad26.COV2.S after at least 2 months. A certain benefit can reasonably be assumed after a homologous boost with Ad26.COV2.S, but this benefit might be limited and is very likely lower than with mRNA heterologous boosting. For the Delta variant, there were no data after a booster given at 2 months post-dose 1, whereas limited data indicate an increase of nAb post-boost when given at 6 months post-dose 1. For heterologous boosting with Ad26.COV2.S after primary vaccination with an mRNA vaccine, the level of nAb at 1 month post-boost is in the same range than after homologous mRNA boosting. The risk of TTS events associated with a booster of Ad26.COV2.S remains unknown.

Although there are many uncertainties and limitations, the benefit risk of booster vaccination with Ad26.COV2.S can be considered positive as reflected in the updated SmPC.

The benefit-risk balance of COVID-19 Vaccine Janssen, remains positive.

9. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC in order to introduce an homologous booster dose (second dose) of COVID-19 vaccine Janssen based on interim efficacy, immunogenicity and safety results from different clinical studies including the two randomised, double blind, placebo-controlled Phase 3 studies COV3001 and COV3009. A contraindication in individuals with a history thrombosis with thrombocytopenia syndrome following vaccination with any COVID-19 vaccine is also included. In addition, an update to introduce an heterologous booster dose of COVID-19 vaccine Janssen following completion of a primary vaccination with an approved mRNA COVID-19 vaccine is introduced based on immunogenicity and safety interim results from the phase 1/2 study DMID 21-0012. In addition, the MAH took the opportunity to update the efficacy data for the primary vaccination schedule based on final analysis from study COV3001. The Package Leaflet is updated accordingly.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Annex: New recommendations introduced in this procedure

General Clinical aspects

1. Results of the primary analysis of study COV2008 are expected to be available by February/March 2022. The data should be shared as soon as availavle.
2. For study COV3009, the full CSR of the final analysis of the double-blind phase (expected in Q1 2022) and the final CSR with the analysis of the open label phase (expected in Q3/4 2022) should be submitted.
3. For study DMID 21-0012, relevant interim analyses data and final analysis data should be submitted when they are made available to the MAH.
4. Results of the CoV-BOOST study should be submitted if data are made available to the MAH.

Clinical Immunology aspects

5. REC related to immunological assays
    a. The MAH is requested to provide results of correlation between the pseudotyped virus neutralization assay (psVNA) of Monogram and the wild-type SARS-CoV-2 VNA (wtVNA) of Public Health England (PHE) in the next report presenting data generated with the psVNA of Monogram.
    b. The plan and timeline for development of both Monogram psVNA and PHE wtVNA for the Omicron variant and for results availability should be communicated to the Agency when available, as proposed by the MAH. Results obtained for Omicron variant should be submitted, as available.
    c. The MAH is requested to provide the qualification and validation reports of the psVNAs of Duke Nab Lab (PI: Dr Montefiori), including for the Delta variant in the next report presenting data of the DMID 21-0012 NIH/NIAID study, if made available to the MAH.
    d. The MAH is requested to provide the qualification and validation reports of the 4-plex and 10-plex ECLIA assays, for the WA-1 and variants, including the Delta, in the next report presenting data of the DMID 21-0012 NIH/NIAID study, if made available to the MAH.
6. The MAH should submit neutralizing and binding Ab data post-dose 2 over more than 1 month for study COV2001, when available.
7. Data on neutralizing capacity of the Delta and Beta variant of the DMID 21-0012 NIH/NIAID study are currently not available. The data should be provided when the analysis is completed, if made available to the MAH.
8. Results of the primary analysis of study COV2008 are expected to be available by February/March 2022. The data should be shared as soon as available. Results obtained with psVNA against the reference strain, Delta and Beta variants are expected.
9. Results of the COV3009 samples from the immunogenicity subset should be shared with the Agency, as available. Results obtained with psVNA against the reference strain, Delta and Beta variants are expected.

10. A literature review of immunogenicity data post-homologous or heterologous boost with COVID-19 Vaccine Janssen or the mRNA vaccines should be submitted regulalry. The first review is expected with the submission of study COV2008.

Clinical efficacy aspects

11. For study COV3001: Additional analyses of incidence rates of / effectiveness against moderate/severe and severe COVID-19 cases accrued during the Delta variant period are planned (double-blind and open-label phases) and should be submitted as soon as available. The format of submission should be discussed with EMA to make sure these data will be submitted as rapidly as possible, given the relevance for the public health.
12. For study COV3001: Efficacy/incidence analyses by variant (double-blind and open-label phase) are planned based on updated genomic sequencing, and should be submitted as soon as available. The format of submission should be discussed with EMA to make sure these data will be submitted as rapidly as possible, given relevance for the public health.
13. For study COV3009: Additional analyses of incidence rates of / effectiveness against moderate/severe and severe COVID-19 cases accrued during the Delta variant period are planned (double-blind and open-label phases) and should be submitted as soon as available. The format of submission should be discussed with EMA to make sure these data will be submitted as rapidly as possible, given relevance for the public health.
14. For study COV3009: Efficacy/incidence analyses by variant (double-blind and open-label phase) are planned based on updated genomic sequencing, and should be submitted as soon as available. The format of submission should be discussed with EMA to make sure these data will be submitted as rapidly as possible, given relevance for the public health.
15. For COV3001 and COV3009: In further analyses of COV3001 and COV3009, the incidence of COVID-19 will be compared across groups during the time period from 01 July 2021 to 21 September 2021 (covering a period where the Delta variant circulated) (REC11 and REC13). Genomic sequencing information will be provided as well to characterize the incidence and (relative) efficacy by variant (REC12 and REC14). This will be done separately for each trial. At the time of reporting, based on more information on the number of participants/cases, the MAH should re-consider pooling both trials data when reporting the efficacy results from these additional analyses, including adjusting for covariates. Moreover, at that time, the MAH should also update the agency with their plans to assess effectiveness of the single dose schedule, effectiveness of the two-dose schedule, and effectiveness of the booster (single vs two-dose schedule), by variants (genomic analyses) and over period during which a predominant variant circulates, including for pooled analyses over trials.
16. The MAH should submit the real-world homologous and heterologous booster data of studies COV4002, COV4004, and Sisonke boost study. Interim and final results should be submitted.
17. The MAH should submit regular overviews of all relevant real-world data of studies where COVID-19 Vaccine Janssen has been used as a single dose, as homologous or as heterologous booster. The overview should include the literature review of published and unpublished reports, and with a special emphasis on effectiveness data against the Delta variant and new emerging VoC such as Omicron, and any other relevant VoC that would emerge. The first overview is expected in 6 months.
18. The MAH is asked to do a regular literature review of efficacy and effectiveness data against asymptomatic infection and transmission, after a single dose or a booster dose of COVID-19

Vaccine Janssen. A summary of the review should be submitted on regular basis. The first review is expected in 6 months.

19. The MAH is asked to do a regular literature review of efficacy and effectiveness data in special populations, such as immunocompromised individuals, who received a single or a booster dose of COVID-19 Vaccine Janssen. A summary of the review should be submitted on regular basis. The first review is expected in 6 months.