

Vaccines and Related Biological Products Advisory Committee Meeting

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JANSSEN BIOTECH, INC.
(A PHARMACEUTICAL COMPANY OF JOHNSON & JOHNSON)

COVID-19 Vaccine Ad26.COV2.S

VAC31518 (JNJ-78436735)

SPONSOR BRIEFING DOCUMENT

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

MEETING DATE: 26 FEBRUARY 2021

TABLE OF CONTENTS

Table of Contents	2
List of Tables	5
List of Figures	7
List of Abbreviations.....	9
1 Executive Summary	11
2 Background on COVID-19.....	25
2.1 Overview of COVID-19	25
2.2 Unmet Medical Need	25
2.3 Current Vaccine Options.....	26
3 Product Description, Platform Data and Candidate selection.....	27
3.1 Product Description	27
3.1.1 AdVac [®] Platform	27
3.1.2 Mechanism of Action.....	28
3.1.3 Vaccine Candidate Selection	29
3.2 Ad26.COV2.S Dose Selection Rationale.....	29
3.3 Proposed Emergency Use Authorization (EUA) Indication Statement.....	30
4 Supporting Nonclinical Investigations	31
4.1 Nonclinical Immunogenicity and Efficacy	31
4.2 Nonclinical Safety	31
4.2.1 Biodistribution	31
4.2.2 Toxicology.....	31
5 Regulatory and Clinical Development Overview	33
5.1 Regulatory Overview	33
5.2 Clinical Development Program: Initiated Studies	33
5.3 Clinical Development Program: Planned Studies	34
6 Clinical Immunogenicity	35
6.1 Assays Used for Immunogenicity Assessments.....	35
6.2 Phase 1/2a Study COV1001	36
6.2.1 Study Design	36
6.2.2 Humoral Immunogenicity	37
6.2.3 Cellular Immunogenicity.....	40

6.3	Phase 1 Study COV1002.....	42
6.4	Phase 2a Study COV2001.....	42
6.5	Phase 3 Study COV3001 Interim Immunogenicity Results.....	43
7	Clinical Efficacy.....	45
7.1	Phase 3 Study COV3001 (ENSEMBLE) – Single Dose Ad26.COV2.S.....	46
7.1.1	Study Design	46
7.1.1.1	Overall Design.....	46
7.1.1.2	Enrollment Criteria	47
7.1.1.3	Independent Review of Severe/Critical COVID-19	48
7.1.1.4	Endpoints.....	48
7.1.1.5	Case Definitions	49
7.1.1.5.1	Case Definition for Moderate COVID-19	49
7.1.1.5.2	Case Definition for Severe/Critical COVID-19	50
7.1.1.5.3	Case Definition for Mild COVID-19.....	51
7.1.1.5.4	US FDA Harmonized Case Definition for COVID-19.....	51
7.1.1.5.5	Case Definition for Asymptomatic or Undetected COVID-19.....	51
7.1.1.6	Statistical Analyses	52
7.1.1.6.1	Sample Size Determination.....	52
7.1.1.6.2	Analysis Populations	52
7.1.1.6.3	Efficacy Analysis.....	53
7.1.2	Epidemiological Setting	54
7.1.3	Participant Disposition.....	55
7.1.4	Participant Demographics	56
7.1.5	Primary Endpoint Results – Moderate and Severe Disease	58
7.1.5.1	Co-Primary Efficacy Results.....	58
7.1.6	Secondary Endpoint Results.....	61
7.1.6.1	Vaccine Efficacy Against Severe/Critical COVID-19	61
7.1.6.2	Prevention of COVID-19 Requiring Medical Intervention	63
7.1.6.3	Prevention of COVID-19-Related Death.....	64
7.1.6.4	Vaccine Efficacy Against All Symptomatic COVID-19 (BOD)	64
7.1.6.5	Vaccine Impact on Symptom Severity	64
7.1.6.6	Vaccine Impact on Asymptomatic COVID-19 Infections as Inferred Through Seroconversion.....	66

7.1.6.7	Effect of Vaccine on SARS-CoV-2 Viral Load	66
7.1.6.8	Vaccine Efficacy Against US FDA Harmonized COVID-19 Definition	66
7.1.7	Efficacy in Subgroups	67
7.1.7.1	Efficacy by Region/Country	67
7.1.7.2	Efficacy by Demographic and Baseline Characteristics: Age, Sex, Race, Ethnicity, Comorbidities and Location	67
7.1.7.3	Efficacy in HIV-Infected Participants	70
7.1.7.4	Efficacy in Regions with Newly Emerging SARS-CoV-2 Strains	70
7.2	Proposed Amendment to Study Design for Placebo-controlled Studies with Ad26.COV2.S After Obtaining EUA	71
8	Clinical Safety and Reactogenicity	73
8.1	Introduction and Methodology	73
8.2	Safety Population	74
8.3	Vaccine Exposure	75
8.4	Adverse Events	76
8.4.1	Solicited Adverse Events	76
8.4.1.1	Solicited Injection Site (Local) Adverse Events	76
8.4.1.2	Solicited Systemic Adverse Events	77
8.4.2	Unsolicited Adverse Events	78
8.4.3	MAAEs, Deaths, SAEs	79
8.4.3.1	Medically-attended Adverse Events	79
8.4.3.2	Deaths	80
8.4.3.3	Serious Adverse Events	81
8.4.4	Vaccine-Associated Enhanced Disease	84
8.4.5	Immediate Adverse Events	85
8.4.6	Adverse Events of Interest	85
8.4.6.1	Allergic Reactions (Hypersensitivity) and Severe Allergic Reactions (Anaphylaxis)	85
8.4.6.2	Tinnitus	86
8.4.6.3	Convulsions/Seizures	86
8.4.6.4	Thrombotic and Thromboembolic Events	87
8.4.6.5	Demyelinating Disorders	87
8.4.6.6	Bell’s Palsy	88

8.4.7	Adverse Events in Subgroups.....	88
8.5	Safety Profile of AdVac® Platform	88
8.6	Additional Safety Data: Other Ongoing Clinical Studies.....	90
9	Pharmacovigilance/Safety Monitoring Plan	92
9.1	Routine Pharmacovigilance	92
9.2	Additional PV Activities.....	93
10	Benefit-Risk Conclusions	95
10.1	Efficacy	95
10.2	Immunogenicity.....	97
10.3	Safety	97
10.4	Conclusion.....	97
11	References.....	99
12	Appendices.....	103
12.1	Appendix: Enrollment Criteria for Phase 3 Study COV3001 (ENSEMBLE).....	103
12.2	Appendix: Additional Demographics	109
12.3	Appendix: Additional Efficacy Displays	111
12.4	Appendix: Adverse Events of Interest.....	114
12.5	Appendix: AdVac® Clinical Exposure and Safety Experience.....	118

List of Tables

Table 1:	Selected Primary and Secondary Endpoints, Per Protocol Population (Study COV3001)	16
Table 2:	SARS-CoV-2 Variant Prevalence in Molecularly Confirmed COVID-19 Cases in COV3001 in the US, South Africa, Brazil	17
Table 3:	Vaccine Efficacy Against Moderate to Severe/Critical COVID-19 and Severe/Critical COVID-19 by Country (Per Protocol Population)	18
Table 4:	Solicited and Unsolicited Adverse Events in Study COV3001 (Safety Subset).....	21
Table 5:	Medically-attended Adverse Events, Serious Adverse Events, and Deaths in Study COV3001.....	22
Table 6:	Deaths Occurring in Study COV3001	23
Table 7:	Overview of Initiated/Ongoing Clinical Studies of Ad26.COV2.S.....	33
Table 8:	Immunological Assays Used for Analysis of Immune Responses in the Ad26.COV2.S Clinical Studies	36

Table 9:	Non-neutralizing Antibody Functionality, as Measured by Antibody-dependent Cellular Phagocytosis in Participants Aged 18-55 Years and 65 Years or Older	39
Table 10:	Global Baseline Demographics and Comorbidities (Study COV3001).....	57
Table 11:	US Baseline Demographics and Comorbidities (Study COV3001)	58
Table 12:	Vaccine Efficacy Against Molecularly Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 Days and at Least 28 Days After Vaccination, Per Protocol Population (Study COV3001).....	59
Table 13:	COVID-19 Requiring Medical Intervention	63
Table 14:	Hospitalization Associated with COVID-19, Not Included in the MRU Form Analysis.....	63
Table 15:	Number of Participants with Unsolicited Adverse Events of at Least Grade 3 and Related to Vaccination by System Organ Class and Preferred Term in COV3001 (Safety Subset).....	79
Table 16:	Listing of Fatal Adverse Events in Study COV3001 (FAS)	81
Table 17:	Serious Adverse Events Related to Vaccination	83
Table 18:	Serious Adverse Events not associated with COVID-19 by System Organ Class in Study COV3001 (FAS).....	84
Table 19:	Distribution of Thrombotic/Thromboembolic Events by Subtype/System Organ Class	87
Table 20:	Additional Global Baseline Demographics and Comorbidities (Study COV3001)	109
Table 21:	Additional US Baseline Demographics and Comorbidities (Study COV3001).....	110
Table 22:	Vaccine Efficacy Against Moderate to Severe/Critical and Severe/Critical COVID-19 by Country, with Absolute Case Numbers (Per Protocol Population)	111
Table 23:	Adverse Events of Interest: Hypersensitivity (Study COV3001).....	114
Table 24:	Adverse Events of Interest: Tinnitus (Study COV3001)	115
Table 25:	Adverse Events of Interest: Seizures/Convulsions (Study COV3001).....	115
Table 26:	Adverse Events of Interest: Deep Vein Thrombosis (Study COV3001)	116
Table 27:	Adverse Events of Interest: Pulmonary Embolism (Study COV3001)	117
Table 28:	AdVac [®] Clinical Exposure and Safety Experience	118

List of Figures

Figure 1: Ad26.COV2.S Clinical Development Program Overview..... 14

Figure 2: Overview of Planned Clinical Studies of Ad26.COV2.S 34

Figure 3: Neutralizing Antibody Titers Induced by a Single Dose of Ad26.COV2.S at 5×10^{10} vp Dose Level In Participants Aged 18-55 and 65 Years or Older. 37

Figure 4: Spike Protein Binding Antibody Concentrations Induced by a Single Dose of Ad26.COV2.S at 5×10^{10} vp Dose Level in Participants Aged 18-55 and 65 Years or Older 38

Figure 5: Th1 and Th2 CD4+ Cell Responses Elicited by a Single Dose of Ad26.COV2.S at the 5×10^{10} vp Dose Level in Participants Aged 18-55 Years and 65 Years or Older..... 41

Figure 6: CD8+ T Cell Responses Elicited by a Single Dose of Ad26.COV2.S at the 5×10^{10} vp Dose Level in Participants Aged 18-55 Years and 65 Years or Older 42

Figure 7: Spike Protein Binding Antibody Concentrations Elicited by a Single Dose of Ad26.COV2.S at 5×10^{10} vp Dose Level in Participants >18 Years of Age from Brazil, South Africa and the US 44

Figure 8: Phase 3 Study COV3001: Study Design..... 46

Figure 9: Phase 3 Study COV3001: Scheduled Visits and Assessments..... 47

Figure 10: Peak Weekly COVID-19 Annualized Incidence in the Placebo Group, Seronegative Participants, of Study COV3001 (FAS)..... 55

Figure 11: Disposition of Participants in Study COV3001..... 56

Figure 12: Cumulative Incidence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases with Onset at Least 1 Day after Vaccination up to Day 126, Full Analysis Set (Study COV3001)..... 60

Figure 13: Vaccine Efficacy Over Time for Molecularly Confirmed Moderate to Severe/Critical Cases (FAS)..... 60

Figure 14: Cumulative Incidence of Molecularly Confirmed Severe/Critical COVID-19 Cases with Onset at Least 1 Day after Vaccination up to Day 126, Full Analysis Set (Study COV3001)..... 62

Figure 15: Vaccine Efficacy Over Time for Molecularly Confirmed Severe/Critical Cases (FAS)..... 62

Figure 16: Summary of Efficacy of first Occurrence of Moderate COVID-19 with Onset at Least 28 Days After Vaccination by Number of Symptoms; Per Protocol Set (Study VAC31518COV3001) 65

Figure 17: Kaplan-Meier Curves of Time on Study by Age and Comorbidities; Per Protocol Analysis Set (VAC31518COV3001)..... 68

Figure 18: Vaccine Efficacy Against Moderate to Severe/Critical COVID-19 at Least 28 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001)	69
Figure 19: Vaccine Efficacy Against Severe/Critical COVID-19 at Least 28 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001)	70
Figure 20: New Designs for Studies COV3001 and COV3009	72
Figure 21: Disposition of the Safety Population and Subset (Study COV3001)	75
Figure 22: Most Frequently Reported Solicited Injection Site (Local) Adverse Events in Study COV3001 (Safety Subset)	77
Figure 23: Most Frequently Reported Solicited Systemic Adverse Events in Study COV3001 (Safety Subset)	78
Figure 24: Vaccine Efficacy Against Moderate to Severe/Critical COVID-19 from at Least 14 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001).....	112
Figure 25: Vaccine Efficacy Against Severe/Critical COVID-19 from at Least 14 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001))	113

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ad26	adenovirus type 26
AdVac®	adenoviral vector vaccine
AE	adverse event
AESI	adverse event of special interest
BARDA	Biomedical Advanced Research and Development Authority
BMI	body mass index
BOD	burden of disease
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CT	computerized tomography
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FAS	Full Analysis Set
Fc	crystallizable fragment
FDA	Food and Drug Administration
FiO ₂	fraction of inspired oxygen
FWER	family-wise error rate
GBS	Guillain-Barré Syndrome
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
HIV	human immunodeficiency virus
IC ₅₀	50% inhibitory concentration
ICU	intensive care unit
IFN- γ	interferon gamma
Ig	immunoglobulin
IM	intramuscular(ly)
LOD	limit of detection
MAAE	medically-attended adverse event
MERS-CoV	Middle East respiratory syndrome coronavirus
MRU	Medical resource utilization
NHP	non-human primate
PaO ₂	partial pressure of oxygen
PCR	polymerase chain reaction
PE	pulmonary embolism
PP	Per-protocol (efficacy)
PPI	Per-protocol Immunogenicity
PT	preferred term
PV	pharmacovigilance
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse-transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event

Abbreviation	Definition
SARS	severe acute respiratory syndrome
SARS-CoV(-2)	severe acute respiratory syndrome coronavirus(-2)
SIC	Symptoms of Infection with Coronavirus-19
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SpO ₂	oxygen saturation
SPRT	sequential probability ratio test
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VNA	virus neutralization assay
vp	virus particles
WHO	World Health Organization
wt	wild-type
wtVNA	wild-type virus neutralization assay

1 EXECUTIVE SUMMARY

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode a stabilized form of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) Spike (S) protein (from the isolate Wuhan-Hu-1, GenBank accession number: MN908947). Ad26.COV2.S is administered as a single dose intramuscular (IM) injection of 5×10^{10} viral particles (vp) in a liquid volume of 0.5 mL.

Janssen Biotech, Inc. (Janssen) is seeking Emergency Use Authorization (EUA) for Ad26.COV2.S for active immunization for the prevention of coronavirus disease 2019 (COVID-19) in adults 18 years of age and older. The authorization request is based on clinical studies with efficacy, immunogenicity, and safety data that support a favorable benefit-risk profile for Ad26.COV2.S as a single dose vaccine.

The Phase 3 study COV3001 examined a single dose of Ad26.COV2.S in a diverse adult population (Table 10) ≥ 18 years of age, including adults ≥ 60 years of age, allowing the following observations after at least 2 months (8 weeks) of follow-up:

- **Ad26.COV2.S is effective against symptomatic COVID-19 and met both co-primary endpoints of the study.**

Vaccine efficacy (VE) (adjusted 95% confidence interval [CI]) for the co-primary endpoints against molecularly confirmed moderate to severe/critical COVID-19 in participants who were seronegative at the time of vaccination was 66.9% (59.03; 73.40) when considering cases diagnosed at least 14 days after vaccination and 66.1% (55.01; 74.80) when considering cases diagnosed from at least 28 days after vaccination. Consistent efficacy is shown across age groups (see Table 1).

- **Ad26.COV2.S is highly effective in the prevention of severe/critical COVID-19** (see Table 1), particularly in prevention of hospitalization and death, across all countries and all ages (see Sections 7.1.6 and 7.1.7).

Vaccine efficacy (adjusted 95% CI) against molecularly confirmed severe/critical COVID-19 diagnosed at least 14 days after vaccination was 76.7% (54.56; 89.09) and increased to 85.4% (54.15; 96.90) at least 28 days after vaccination (see Table 1). The vaccine prevented COVID-19-related medical interventions (defined as hospitalization, ICU admission, mechanical ventilation, ECMO; 0 vs 7 participants in the Ad26.COV2.S and placebo groups, respectively) and COVID-19-related death (0 vs 5 deaths in the Ad26.COV2.S and placebo groups, respectively) at least 28 days after vaccination.

- **Ad26.COV2.S is effective in preventing symptomatic COVID-19 in the United States (US) population.**

In the US, VE (95% CI) against moderate to severe/critical COVID-19 was 74.4% (65.00; 81.57) and 72.0% (58.19; 81.71) at least 14 days and at least 28 days after vaccination, respectively. Vaccine efficacy (95% CI) against severe/critical COVID-19 in the US was 78.0% (33.13; 94.58) at least 14 days and 85.9% (-9.38; 99.69) at least 28 days after vaccination (see Table 3).

- **Ad26.COV2.S is highly effective in the prevention of severe/critical COVID-19 caused by newly emerging strains**, such as the 20H/501Y.V2 strain.

In South Africa, VE (95% CI) against severe/critical COVID-19 occurring at least 14 days after vaccination was 73.1% (40.03, 89.36) and increased to 81.7% (46.18, 95.42) at least 28 days after vaccination (see Table 3). Based on sequences available, it is estimated that >90% of cases in South Africa were caused by 20H/501Y.V2 (see Table 3).

- **Breakthrough infections of COVID-19 in vaccinated participants were milder** (see Section 7.1.6.5).
- **Preliminary data suggest that there is protection against asymptomatic COVID-19** as inferred through asymptomatic seroconversion (see Section 7.1.6.6).
- **Ad26.COV2.S has an acceptable safety and reactogenicity profile** in adults aged ≥ 18 years, including adults aged ≥ 60 years, regardless of prior SARS-CoV-2 infection (see Section 8).

Product Description

Janssen has developed Ad26.COV2.S based on the AdVac[®] technology platform. In other disease areas, Ad26-based vaccines based on this platform have been shown to induce robust and durable immune responses, both humoral and cellular, with a favorable safety profile. The Ad26 vector cannot replicate following administration to humans, and available data demonstrate that it is cleared from tissues following injection.

Ad26 was selected as the vector for the COVID-19 vaccine because it is a flexible platform, allows for production at large scale and can be rapidly adapted for new antigens. There is also substantial nonclinical and clinical experience with Janssen's Ad26-based vaccines that demonstrate a capacity to elicit strong humoral (antibody) and cellular (CD4⁺ T-cells, CD8⁺ T-cells, including memory T cells) immune responses against disparate viral pathogens. Humoral immune responses consist of neutralizing antibodies and/or antibodies with other Fc mediated effector functions. The CD4⁺ T helper cell responses are predominantly of the Th1-phenotype, supporting production of immunoglobulins and maturation of B cells, and this predominance is considered important to prevent predisposition to vaccine-associated enhanced respiratory disease (VAERD). CD8⁺ T-cells are important in clearing virus-infected cells. The memory phenotype of vaccine-antigen specific T-cells is present already after one dose of AdVac-based vaccine candidates and likely contributes to the durability of protection.

Ad26.COV2.S:

- delivers a transgene encoding the S protein of SARS-CoV-2 with two proline mutations and a knock-out of the furin cleavage site for optimal stability in its pre-fusion conformation.
- does not contain preservatives nor require reconstitution.
- can be stored for at least 3 months at normal refrigerator temperatures of 2° C to 8° C (36°F to 46°F). The vaccine can also be kept at -25° C to -15° C (-13°F to 5°F) for long term

storage (see Section 3.1, 24 months long-term shelf life). Its shipping and storage fits into the existing medical supply infrastructure.

- offers the potential for rapid vaccination of a population due to the proposed single-dose administration regimen.

Clinical Development Program

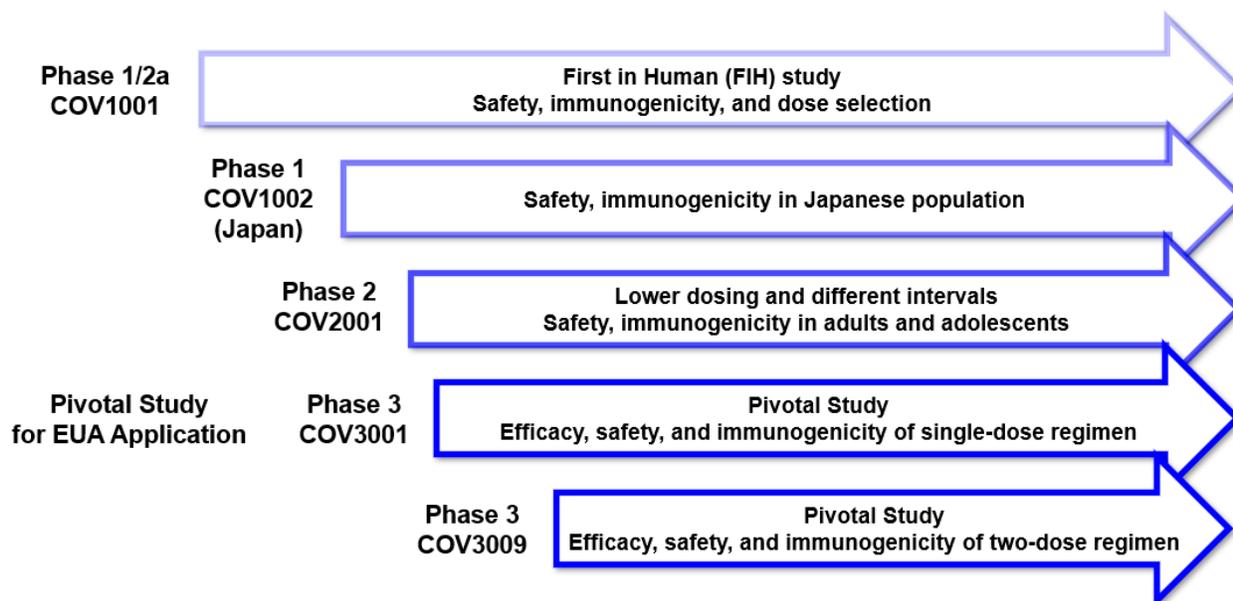
Janssen is conducting a comprehensive clinical program for Ad26.COV2.S, with five ongoing studies (see Figure 1).

- Study COV1001 is a first-in-human Phase 1/2a randomized, double-blind, placebo-controlled, safety, immunogenicity, and dose selection study. The findings supported the selection of the single dose regimen of 5×10^{10} vp for use in the pivotal Phase 3 study COV3001.
- Study COV1002 is an additional Phase 1 study in Japan evaluating the safety and immunogenicity of two different dose levels (5×10^{10} vp and 1×10^{11} vp).
- Study COV2001 is a Phase 2a study in adults and adolescents aged ≥ 12 to ≤ 17 years, investigating a range of dosing regimens, as well as assessing safety and immunogenicity.
- Study COV3001 is a pivotal Phase 3 study examining the efficacy, safety, and immunogenicity of the selected single dose regimen. This study is fully enrolled with more than 43,000 participants vaccinated.
- Study COV3009 is a pivotal Phase 3 study that is evaluating the efficacy, safety, and immunogenicity of a 2-dose regimen.

Studies in other populations (ie, pregnant women, children with and without comorbidities) are also planned (see Figure 2).

This briefing document focuses on the Phase 1/2a and Phase 3 studies investigating the safety, immunogenicity, and efficacy of a single-dose of Ad26.COV2.S in participants 18 years of age and older.

Figure 1: Ad26.COV2.S Clinical Development Program Overview



Phase 1/2a Immunogenicity Summary (COV1001)

Data from this study demonstrate that a single dose of Ad26.COV2.S elicited SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 Spike binding antibody responses that were detected by Day 15, increased to Day 57 and maintained until at least Day 85 across age groups. Cellular responses to Ad26.COV2.S were detected in the vast majority of participants at Day 15 and consisted of CD8+ T cell responses as well as predominantly Th1 CD4+ T cell responses. Neutralizing and binding antibody responses are maintained to at least Day 85 for participants 18-55 years old, and responses show no significant waning for participants of 65 years and older. These results are consistent with immune responses and durability observed with the Ad26-vector platform data and with nonclinical data with Ad26.COV2.S. Non-clinical data showing durable antibody responses up to 6 months post dose in NHPs are described in Section 4.1.

Phase 3 Efficacy Results (COV3001)

Study COV3001 is an ongoing, multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy, safety, and immunogenicity of a single dose (5×10^{10} vp) of Ad26.COV2.S for the prevention of COVID-19 in adults aged 18 years and older. The study is being conducted in the US, South Africa, Brazil, Chile, Argentina, Colombia, Peru, and Mexico. A total of 44,325 participants were randomized of whom 43,783 were vaccinated with either Ad26.COV2.S or placebo. The study is well-balanced among subgroups with regard to age, comorbidities, sex, region, race, and ethnicity (see Table 10). The study was initiated at sites expected to experience high incidence of COVID-19 on 21 September 2020, shortly before the incidence of COVID-19 increased substantially across the globe (see Figure 10). The time of study enrollment coincided with the emergence of new SARS-CoV-2 variants, which were emerging in some of the countries where study COV3001 was being conducted. Efficacy results were based on

the primary analysis, which included 19,630 participants who received Ad26.COV2.S and 19,691 participants who received placebo. For descriptions of study analysis populations and case definitions, see Sections 7.1.1.6.2 and 7.1.1.5, respectively.

The co-primary endpoints in study COV3001 evaluated the first occurrence of molecularly confirmed COVID-19, including both moderate and severe/critical COVID-19 cases according to their case definitions (see Section 7.1.1.5), with onset at least 14 days or at least 28 days after vaccination with Ad26.COV2.S versus placebo. All other efficacy endpoints were also evaluated at 14 days and 28 days after vaccination. The primary efficacy analysis was performed after 50% of the participants had been followed for 8 weeks from the day of vaccination, on 22 January 2021, with 464 primary endpoint cases at least 14 days after vaccination and 259 primary endpoint cases at least 28 days after vaccination. The total number of symptomatic cases (468 at least 14 days after vaccination and 261 at least 28 days after vaccination) was very similar to the total number of moderate and severe/critical COVID-19 cases. Participants are planned to be followed up for up to 24 months, for assessments of both safety and efficacy against COVID-19. Following the EUA, Janssen proposes to change the study design of study COV3001, offering a single dose of Ad26.COV2.S to participants who initially received placebo, resulting in de facto unblinding of participants and investigators (see details in Section 7.2).

The Phase 3 study COV3001 was successful in demonstrating Ad26.COV2.S efficacy for both co-primary endpoints. A single dose of Ad26.COV2.S protected against moderate to severe/critical COVID-19 in adults ≥ 18 years of age, including adults ≥ 60 years of age, with an efficacy that was consistent across age groups (see Table 1) but with some variability across countries (Table 3).

The vaccine was highly efficacious against severe/critical COVID-19. Efficacy was consistently high across age groups, regions, and countries (see Table 1, Table 3, Figure 19, and Section 7.1.7.4). As a prespecified secondary endpoint, the vaccine also prevented COVID-19 requiring medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, ECMO linked to objective measures such as decreased oxygenation, X-ray or CT findings) (see Table 13) and COVID-19-related deaths, with all post-Day 28 hospitalization and deaths occurring in the placebo group.

Vaccine efficacy against moderate to severe/critical COVID-19 and severe/critical COVID-19 by country, with absolute numbers for cases, is presented in Table 22 in Appendix 12.3.

Table 1: Selected Primary and Secondary Endpoints, Per Protocol Population (Study COV3001)

Per Protocol (PP)	Day 14			Day 28		
	Ad26.COVS.2.S N=19,630	Placebo N=19,691	VE (95% CI) ^a	Ad26.COVS.2.S N=19,630	Placebo N=19,691	VE (95% CI) ^a
Per Protocol At Risk set ^b	19,514	19,544		19,306	19,178	
Primary endpoints (PCR+ by central laboratory)^c	# Cases	# Cases		# Cases	# Cases	
Moderate to severe/critical	116	348	66.9% *(59.03; 73.40)	66	193	66.1% *(55.01; 74.80)
Secondary endpoints (PCR+ by central laboratory)^c	# Cases	# Cases		# Cases	# Cases	
Any symptomatic COVID-19 severity	117	351	66.9% (59.1, 73.4)	66	195	66.5% (55.5, 75.1)
Mild	1	3		0	2	
Moderate	102	288	64.8% (55.8, 72.2)	61	159	62.0% (48.7, 72.2)
Severe/critical	14	60	76.7% *(54.6, 89.1)	5	34	85.4% *(54.2, 96.9)
All symptomatic COVID-19 (BOD) ^e	117	351	68.1% *(60.3, 74.3)	66	195	69.0% *(56.7, 77.6)
Age 18-59 years	95	260	65.8% (56.2, 73.1)	52	152	69.3% (57.4, 77.7)
Age ≥60 years	22	91	74.5% (57.9, 84.3)	14	43	67.9% (38.2, 82.8)
Supplemental Endpoints	# Cases	# Cases		# Cases	# Cases	
Co-primary endpoints including cases that were PCR+ from any source ^d	173	509	66.3% *(59.9, 71.8)	113	324	65.5% *(57.2, 72.4)
US FDA Harmonized COVID-19 cases	114	345	67.2% (59.3, 73.7)	65	193	66.7% (55.6, 75.2)

* Adjusted 95% CI

^a The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.

^b The risk set are all participants of the Per Protocol Set excluding participants that had a positive PCR test between Day 1 and Day 14 or Day 28.

^c Analysis based on a data set of centrally confirmed COVID-19 cases.

^d Analysis based on a data set including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation.

^e BOD: Burden of Disease is a weighted version of the mild, moderate, and severe/critical vaccine efficacies.

In the US, where newly emerging strains were not predominant, VE against moderate to severe/critical COVID-19 and against severe/critical COVID-19 was consistent with the global VE findings. In South Africa, where the 20H/501Y.V2 variant (B.1.351 lineage) was the predominant strain (96.3% of sequenced cases thus far), high efficacy was observed against severe/critical COVID-19 (81.7% [95% CI: 46.2, 95.4] at least 28 days after vaccination) and robust VE was observed for moderate to severe/critical COVID-19 (64.0% [95% CI: 41.2, 78.7] at least 28 days after vaccination). In Brazil, where a variant from the P.2 lineage was the predominant strain (70.7% of sequenced cases thus far), VE estimates were higher than those in South Africa and similar to those in the US. No differences were observed in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S between participants from Brazil, South Africa, and the US (see Section 6.5). See Table 2 for an overview of SARS-CoV-2 variant prevalence in these regions in molecularly confirmed COVID-19 cases in study COV3001 and refer to Table 3 for an overview of VE by region.

Table 2: SARS-CoV-2 Variant Prevalence in Molecularly Confirmed COVID-19 Cases in COV3001 in the US, South Africa, Brazil

Country	Molecularly Confirmed Cases	Molecularly Confirmed Cases with Sequence data (%)	Variant SARS-CoV-2 Distribution Over Sequenced Cases
US	268	135 (50%)	130 with D614G (96.3%) 4 with CAL.20C (3%) 1 with variant of P.2 lineage (0.7%)
South Africa	136	80 (59%)	77 with 20H/501Y.V2 (96.3%) 2 with D614G (2.5 %) 1 with variant of P.2 lineage (1%)
Brazil	179	82 (46%)	58 with variant of P.2 lineage (70.7%) 24 with D614G (29.3%)

Table 3: Vaccine Efficacy Against Moderate to Severe/Critical COVID-19 and Severe/Critical COVID-19 by Country (Per Protocol Population)

PCR+ by central laboratory ^a			
Country	Onset	Severity	
		Moderate to Severe/Critical Point Estimate (95% CI)	Severe/Critical Point Estimate (95% CI)
Global	≥14 days after vaccination	66.9% (59.0, 73.4)*	76.7% (54.6, 89.1)*
	≥28 days after vaccination	66.1% (55.0, 74.8)*	85.4% (54.2, 96.9)*
PCR+ from any source ^b			
Country	Onset	Severity	
		Moderate to Severe/Critical Point Estimate (95% CI)	Severe/Critical Point Estimate (95% CI)
Global	≥14 days after vaccination	66.3% (59.9, 71.8)*	76.3% (57.9, 87.5)*
	≥28 days after vaccination	65.5% (57.2, 72.4)*	83.5% (54.2, 96.9)*
US	≥14 days after vaccination	74.4% (65.0, 81.6)	78.0% (33.1, 94.6)
	≥28 days after vaccination	72.0% (58.2, 81.7)	85.9% (-9.4, 99.7)
Brazil	≥14 days after vaccination	66.2% (51.0, 77.1)	81.9% (17.0, 98.1)
	≥28 days after vaccination	68.1% (48.8, 80.7)	87.6% (7.8, 99.7)
South Africa	≥14 days after vaccination	52.0% (30.3, 67.4)	73.1% (40.0, 89.4)
	≥28 days after vaccination	64.0% (41.2, 78.7)	81.7% (46.2, 95.4)

*Adjusted 95% CI

^a Analysis based on a data set of centrally confirmed COVID-19 cases.

^b Analysis based on a data set including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation.

The onset of efficacy against moderate to severe/critical COVID-19 was observed at 14 days after vaccination, which persisted for the current duration of follow-up (median 58 days). The case splits for severe/critical COVID-19 in the Ad26.COVS.2.S vs placebo group virtually eliminates the risk of vaccine-associated enhanced disease (VAED), consistent with the Th1 skewed immunologic response. The onset of efficacy against severe/critical COVID-19 was observed at 7 days after vaccination, with a clear trend for increasing VE that persisted for the current duration of follow-up (median 58 days). This rise in VE is consistent with available immunogenicity results from Phase 1/2a (see Section 6.2). Participants with moderate COVID-19 in the Ad26.COVS.2.S group experienced fewer and less severe symptoms than in the placebo group (see Section 7.1.6.5).

Preliminary data, based on a limited number of Day 71 results, suggest a vaccine effect against asymptomatic infection (See Section 7.1.1.5.5).

There were only a limited number of 7 symptomatic cases of COVID-19 observed in participants who were SARS-CoV-2 seropositive at baseline, so it is not possible to provide meaningful comments on the VE in these participants as of yet.

The VE was consistent between sexes, between Hispanic and non-Hispanic, Black/African American and White participants, age groups, and in participants with and without comorbidities (see Section 7.1.7). Analyses of VE in participants ≥ 60 years of age with or without comorbidities may be confounded by small numbers and differences in follow-up time (see Section 7.1.7.2).

At the time of the primary analysis, 464 central laboratory-confirmed primary endpoint cases were observed with an onset at least 14 days after vaccination. Due to the high in-study incidence of COVID-19 and the time it takes for central laboratory confirmation of the local PCR test, not all cases could be confirmed by the central laboratory at the time of the primary analysis. As a result, there were two data sets: a data set of centrally confirmed primary endpoint COVID-19 cases (464 primary endpoint cases after Day 14, 259 after Day 28) and a data set including all primary endpoint COVID-19 cases with a positive PCR from any source, regardless of central confirmation (682 primary endpoint cases after Day 14, 437 after Day 28). Differences in VE estimates based on the two data sets were $<1\%$ and had similar CIs. Among those cases that have completed the central confirmation process, a high concordance was observed (90.3%). For subgroup analyses, COVID-19 requiring medical intervention, and COVID-19 related deaths, the data set including non-centrally confirmed cases was used to increase the robustness of conclusions (Section 7). The primary analysis included centrally confirmed cases only.

Phase 3 Safety Findings (COV3001)

Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥ 18 years of age, including adults ≥ 60 years of age (including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19). In line with other Ad26-based vaccines, hypersensitivity reactions following immunization with Ad26.COV2.S were rare and usually nonserious. Severe allergic (anaphylactic) reactions have not been reported in Ad26.COV2.S clinical studies.

In general, lower reactogenicity was observed in older adults compared to younger adults. Otherwise, no clinically relevant difference in the reactogenicity profile of Ad26.COV2.S was observed by sex, race, ethnicity, geography, comorbidity, SARS-CoV-2 or HIV serostatus at baseline (although numbers in some of these subgroups were too low to draw firm conclusions). Reactogenicity was demonstrated to be transient and most solicited adverse events (AEs) generally resolved in one to two days post vaccination. No Grade 4 solicited local AEs were reported.

Among the 43,783 participants who received a single dose of Ad26.COV2.S at 5×10^{10} vp in the pivotal Phase 3 study, the median follow-up after vaccination was 58 days, and 23,903 (54.6%) participants had at least 2 months (8 weeks) of follow-up at the time of the primary analysis. In the Safety Subset of 6,736 vaccinated participants, 99.9% of the participants in each vaccine group completed the post-vaccination follow-up period of Day 1-29. Longer safety follow-up of >2 months is available for more than 23,000 participants in the Full Analysis Set (FAS) (11,948 participants in the Ad26.COV2.S group and 11,955 in the placebo group).

The safety subset data included both solicited AEs collected from the day of vaccination until 7 days afterwards and unsolicited AEs collected from the day of vaccination until 28 days

afterwards. Data on medically-attended adverse events (MAAEs), serious adverse events (SAEs) and deaths were collected from all 43,783 participants who received a study vaccination and will continue to be collected until end of the study.

Frequencies of solicited and unsolicited AEs are described in Table 4.

In general, solicited AEs (both local and systemic) occurred in a higher frequency in participants in the Ad26.COV2.S group compared to participants in the placebo group. Regardless of the group, most solicited AEs were Grade 1 or 2 in severity and were transient in nature. No Grade 4 (serious) solicited AEs were reported during the study. The most frequently reported Grade 3 solicited local AE was vaccination site pain, reported in 11 (0.3%) participants in the Ad26.COV2.S group.

Grade 3 solicited systemic AEs were reported in <2.0% of participants in the Ad26.COV2.S group. Pyrexia of any grade was reported by 302 (9.0%) and Grade 3 pyrexia was reported by 8 (0.2%) participants in the Ad26.COV2.S group, of which the majority occurred in the younger age group (below 35 years of age). A total 5.2% participants in the Ad26.COV2.S group used analgesics or antipyretics up to 7 days post vaccination.

Overall, there was no apparent difference in unsolicited AEs reported in the Ad26.COV2.S group compared to the placebo group. The most frequently reported unsolicited AEs by preferred term (PT) ($\geq 1.0\%$ of participants in the Ad26.COV2.S group) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs ($\geq 1.0\%$ of participants in the Ad26.COV2.S group), not recorded as solicited AEs were chills, arthralgia, cough, nasal congestion, and diarrhea. Most were of mild or moderate severity and most were considered not related to the study vaccine by the investigator. Other unsolicited AEs were reported in <1.0% of participants in the Ad26.COV2.S group.

The frequency of unsolicited AEs that were considered related to study vaccine by the investigator was higher in participants in the Ad26.COV2.S group (242/440 [55%]) compared to participants in the placebo group (154/407 [37.8%]).

Table 4: Solicited and Unsolicited Adverse Events in Study COV3001 (Safety Subset)

<i>Reported through January 22, 2021</i>	Ad26.COV2.S N =3,356		Placebo N=3,380	
	n	%	n	%
Any Solicited Local Adverse Event (AE)	1687	50.3%	658	19.5%
Grade 3	23	0.7%	6	0.2%
Grade 3 Erythema	7	0.2%	2	0.1%
Grade 3 Pain	11	0.3%	2	0.1%
Grade 3 Swelling	7	0.2%	2	0.1%
Grade 4	0	-	0	-
Any Solicited Systemic AE	1853	55.2%	1188	35.1%
Grade 3	61	1.8%	21	0.6%
Grade 3 Fatigue	35	0.1%	9	0.3%
Grade 3 Headache	23	0.7%	9	0.3%
Grade 3 Myalgia	32	1.0%	6	0.2%
Grade 3 Nausea	6	0.2%	6	0.2%
Grade 3 Pyrexia	8	0.2%	4	0.1%
Grade 4	0	-	0	-
Any Unsolicited AE	440	13.1%	407	12.0%
Grade 3	16	0.5%	16	0.5%
Grade 4	3	0.1%	2	0.1%
≥Grade 3 related	5	0.1%	1	0.1%

Overall, MAAEs, SAEs and deaths were recorded at a higher proportion in the placebo group (Table 5). The most frequently reported MAAE ($\geq 0.5\%$ of participants in any vaccine group) was COVID-19 infection reported for 16 (0.1%) participants in the Ad26.COV2.S group compared to 35 (0.2%) participants in the placebo group. A numerical imbalance was observed in the overall number of non-fatal SAEs between the Ad26.COV2.S group (90) and placebo group (137) due to COVID-19 associated SAEs. Excluding these cases, similar rates of SAEs were reported in the Ad26.COV2.S and placebo group (83 [0.4%] and 96 [0.4%], respectively). Among the SAEs not associated with COVID-19, no imbalances were observed by system organ class (SOC). Of the 227 participants that reported one or more SAEs in the FAS, a total of 10 SAEs in 9 participants were considered by the investigator as related to the study vaccine/placebo (7 events in 7 participants in Ad26.COV2.S group and 3 events in 2 participants in placebo group) (Table 17).

There were no notable patterns or numerical imbalances between the Ad26.COV2.S and placebo group for specific categories of (serious) AEs of interest (including neurologic, neuroinflammatory, and cardiovascular events) that would suggest a causal relationship to the Ad26.COV2.S vaccine. There were numerically more cases of tinnitus, convulsions/seizures, and pulmonary embolism (PE)/deep vein thrombosis (DVT) in the Ad26.COV2.S group. However, in the majority of the cases the participants had one or more underlying medical conditions that are known risk factors for the event in question. In the absence of any signal in the AdVac safety database for these events of interest, and given that the total number of cases observed in the study is low and within the rates observed in the general population, Janssen does not consider these events causally related to the vaccine (Section 8.4.6).

Table 5: Medically-attended Adverse Events, Serious Adverse Events, and Deaths in Study COV3001

<i>Reported through 22 January 2021</i>	Ad26.COVS.2		Placebo	
	n	%	n	%
FAS	N=21,895		N=21,888	
Any medically-attended adverse event (MAAE)	304	1.4%	408	1.9%
Any serious adverse event (SAE)	90	0.4%	137	0.6%
Any non-COVID-19 associated SAE	83	0.4%	96	0.4%
AE of interest**	140	0.6%	134	0.6%
Any death	3	<0.1%	16	<0.1%
Any COVID-19 associated death	0		6*	<0.1%

* One participant had a positive SARS-CoV-2 PCR test result at baseline

**AEs of interest that represent various diseases and conditions including, but not limited to immune-mediated and (neuro-)inflammatory events (eg, Guillain-Barré Syndrome, Bell’s palsy) and thrombotic and thromboembolic events (eg, pulmonary embolism, deep vein thrombosis) – not prespecified analysis

Overall, 19 deaths were reported in study COV3001: 3 in the Ad26.COVS.2 group (lung abscess, non-COVID-19 pneumonia, and one of unknown cause [onset on Day 45]) and 16 in the placebo group, none of which were considered related to the study vaccine by the investigator.

Six of the 16 deaths in the placebo group were confirmed (by positive RT-PCR test) to be associated with COVID-19. It should be noted however, that one of the deaths in the placebo group was reported as COVID-19 pneumonia which had an onset 10 days post vaccination and had a positive PCR test result at baseline. None of the three deaths in the Ad26.COVS.2 group were associated with COVID-19 (Table 6).

For those deaths for which no SARS-CoV-2 RT-PCR test result was available, the likelihood of fatal SAEs being associated with COVID-19 was assessed based on the available information (narratives by the investigator, laboratory data, and reported clinical symptoms) against the WHO COVID-19 case definition (suspected, probable, confirmed COVID-19 events [not deaths])[1]. Cases not meeting the criteria for COVID-19 were classified as “Not COVID-19”.

Out of the 16 deaths reported in the placebo group, six cases were classified as “Confirmed COVID-19” based on WHO case definition and an additional two were classified as “Probable COVID-19”. There were no cases classified as suspected according to the WHO criteria.

The remainder of the deaths in the Ad26.COVS.2 group and placebo group were assessed as “Not-COVID-19” based on the WHO case definition. The imbalance in terms of COVID-19 associated deaths is consistent with the clinical database findings in terms of severity of COVID-19 in the Ad26.COVS.2 group versus the placebo group.

Table 6: Deaths Occurring in Study COV3001

	Clinical database COV3001		
	Ad26.COVS.S	Placebo	Total
Any death	3	16	19
COVID-19 associated ^a	0	6 ^b	6 ^b
Other	3	10	13
	Independent assessment using WHO criteria for COVID-19 cases		
	Ad26.COVS.S	Placebo	Total
Any death	3	16	19
Confirmed COVID-19 ^c	0	6	6
Probable COVID-19 ^c	0	2	2
Not COVID-19 ^c	3	8	11

^a SARS-CoV-2 RT-PCR confirmed COVID-19 case

^b One case had positive SARS-CoV-2 RT-PCR test at baseline

^c WHO COVID-19: Case Definitions. Updated in Public health surveillance for COVID-19, published 16 December 2020 [1].

Importantly, nonclinical and clinical data of Ad26.COVS.S did not indicate any evidence of VAED, including VAERD. For instance, the case splits for COVID-19 associated SAEs and deaths in the Ad26.COVS.S versus the placebo group, virtually eliminates the risk of VAED, consistent with the Th1-skewed immunologic response. These findings confirm that the theoretical risk of VAED, including VAERD, is low.

The general safety findings are further substantiated by the long term and robust platform data demonstrating an acceptable long-term safety and reactogenicity profile for Janssen’s other Ad26-based vaccines, including data from Ebola, HIV, malaria, RSV and filovirus vaccine programs [2].

In summary, Ad26.COVS.S, given as a single dose, is found to have an acceptable safety and reactogenicity profile in adults ≥18 years of age and did not raise safety concerns in any of the assessed populations that are reflective of the target groups for vaccination, including adults ≥60 years of age and adults with comorbidities (including comorbidities associated with an increased risk of progressing to severe/critical COVID-19).

Benefit-risk Summary

Overall, the results demonstrate that: (1) a single dose of Ad26.COVS.S is effective against symptomatic COVID-19; (2) a single dose of Ad26.COVS.S is highly effective in the prevention of severe/critical COVID-19, particularly in prevention of hospitalization and death, across all countries, and ages; and (3) a single dose of Ad26.COVS.S is highly effective against severe disease, hospitalization and death caused by newly emerging strains, such as the 20H/501Y.V2 variant first observed in South Africa and the P.2 variant first observed in Brazil. This high-level

protection against consequential COVID-19 is reassuring since it can be expected that more variants will occur over time.

Use of this vaccine could help control the pandemic, reduce the burden of disease and relieve pressure on the health care infrastructure, in view of its high efficacy in prevention of severe/critical COVID-19, especially hospitalization and death. In addition, the favorable storage conditions and single dose regimen will simplify deployment of vaccination.

The efficacy, immunogenicity and safety data presented in this application support a favorable benefit-risk profile for Ad26.COV2.S in the proposed EUA indication, ie, for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults ≥ 18 years of age.

2 BACKGROUND ON COVID-19

Summary

- As of 22 January 2021, there have been more than 95 million cases of COVID-19 and 2 million deaths due to COVID-19 worldwide [3]. Approximately 26.6 million cases have been reported and the cumulative rate of hospitalizations associated with COVID-19 is more than 450 per 100,000 population, creating an overwhelming burden on the worldwide healthcare systems, including in the US.
- There remains an urgent unmet medical need for additional vaccine availability to expeditiously vaccinate the population and control the COVID-19 pandemic. These vaccines also need to protect against the new variants of SARS-CoV-2 that have been emerging.
- A single-dose, refrigerator temperature-stable vaccine offers greater potential for mass vaccination.
- Janssen's Ad26.COV2.S vaccine candidate is an effective single-dose vaccine that could greatly aid in the efforts for widespread vaccination and reduce the burden of COVID-19 on the healthcare infrastructure and COVID-19 related deaths.

2.1 Overview of COVID-19

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory syndrome (caused by MERS-CoV) and Severe Acute Respiratory Syndrome (caused by SARS-CoV).

An outbreak of COVID-19, caused by the novel SARS-CoV-2, began in Wuhan, Hubei Province, China in December 2019 and has since spread globally [4]. New SARS-CoV-2 variants, with amino acid substitutions also in the S protein that is targeted by vaccines, have emerged and are spreading, in several geographies already replacing the original SARS-CoV-2 variant [5].

2.2 Unmet Medical Need

On 4 February 2020, the Secretary of the US Department of Health and Human Services determined that there is a public health emergency that has a significant potential to affect national security or the health and security of US citizens living abroad, and that involves the virus that causes COVID-19 [6]. On the basis of this determination, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act, effective 27 March 2020 [7].

As of 22 January 2021, over 95 million cases and over 2 million deaths from COVID-19 have been reported worldwide [8] with over 24 million cases and over 400,000 deaths reported across the US [9]. On the same date, the 7-day moving average daily number of new cases and deaths across the US as reported to Centers for Disease Control and Prevention (CDC) was approximately 190,000 new cases and 3,000 new deaths, respectively [3]. The overall cumulative COVID-19-associated

hospitalization rate through the week ending 23 January 2021 was exceeding 400 per 100,000 population [3, 10].

While SARS-CoV2 infected individuals may remain asymptomatic, clinical manifestations range from mild symptoms to severe illness and death [11]. Individuals aged ≥ 65 years, especially those with comorbidities such as cancer, cardiovascular disease, type 2 diabetes mellitus, (severe) obesity, hypertension, chronic kidney disease, and underlying pulmonary disease, are at highest risk for severe disease and death [12-14].

2.3 Current Vaccine Options

Two COVID-19 vaccines have been authorized by the FDA for emergency use in the US (the mRNA-based BNT162b2 vaccine from Pfizer and BioNTech and the mRNA-1273 vaccine from Moderna, Inc.). However, vaccine demand is far exceeding current supplies. As such, an urgent need remains to broaden vaccine availability as the virus continues to spread, with highly transmissible variants continuing to emerge around the globe, also in the US. The Janssen COVID-19 vaccine candidate, being single-dose, easily transportable and stored, and compatible with standard vaccine distribution channels could aid to the further enhancement of the response, to control this pandemic.

3 PRODUCT DESCRIPTION, PLATFORM DATA AND CANDIDATE SELECTION

Summary

- Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent Ad26 vector, constructed to encode a stabilized variant of the SARS-CoV-2 Spike (S) protein.
- The Ad26 vector belongs to Janssen's established AdVac® vaccine platform which has the following characteristics:
 - Non-replicating viral vector vaccine platform
 - High-capacity manufacturing on human complementing cell lines
 - Storage and transport compatible with existing vaccine supply chains
 - More than 193,000 participants vaccinated in clinical studies and vaccination programs as of 31 December 2020
 - Acceptable clinical safety profile and induction of strong humoral and cellular immune responses with a clear Th1 profile
- The design of the Phase 1 study COV1001 was based on AdVac platform experience.
- The proposed vaccine regimen is based on AdVac platform experience and the clinical data with Ad26.COV2.S. A single immunization at a dose level of 5×10^{10} vp of Ad26.COV2.S was selected.

3.1 Product Description

The Ad26.COV2.S product is supplied as a sterile liquid suspension for injection with a target concentration of 1.0×10^{11} vp/mL. Each multi-dose vial contains a fill volume of 3.1 mL to allow for an extractable volume of 2.5 mL as 5 extractions of 0.5 mL. Ad26.COV2.S is administered IM as a single dose. Based on current data, the shelf life of the Ad26.COV2.S drug product is 24 months when stored frozen at -25°C to -15°C (-13°F to 5°F), and within these 24 months, 3 months when stored at 2°C to 8°C (36°F to 46°F).

3.1.1 AdVac® Platform

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human Ad26 vector, constructed to encode the SARS-CoV-2 S protein sequence (from the isolate Wuhan-Hu-1, GenBank accession number: MN908947), stabilized in its prefusion conformation.

Adenoviruses are nonenveloped viruses composed of an icosahedral nucleocapsid and a single double-stranded linear DNA genome. There are at least 88 human adenovirus types [15], divided into subgroups A-G based on neutralization by antisera, and genotyping.

Recombinant, replication-incompetent adenoviral vectors are attractive candidates for expression of foreign genes for a number of reasons. The adenoviral genome is well-characterized and

comparatively easy to manipulate. The AdVac[®] vector platform, consisting of E1/E3-deleted Ad26 vectors in combination with a proprietary human complementing cell line, allows for high-yield production of replication-incompetent adenoviral vector-based vaccines, with transgenes of choice.

Janssen selected Ad26 as the vector for the COVID-19 vaccine because of the substantial nonclinical and clinical evidence from Janssen's other vaccine development programs that also make use of Ad26. As of 31 December 2020, more than 193,000 participants, including people from different age groups (elderly, children and infants), HIV-positive individuals, pregnant and breast-feeding women, have been vaccinated with Ad26-based vaccines in several completed and ongoing clinical studies and vaccination programs, revealing a favorable safety profile. Across programs, Ad26-based vaccines demonstrate the capacity to elicit strong humoral immune responses with both neutralizing activity and non-neutralizing antibody functionalities, and cellular immune responses involving both CD8+ T cells and CD4+ T cells, the latter with predominantly a Th1 phenotype, irrespective of the transgene encoded immunogens [16-26].

In July 2020, the first Ad26-based vaccine was granted Marketing Authorization in Europe by the European Commission. Zabdeno[®] (Ad26.ZEBOV), as part of the Zabdeno, Mvabea vaccine regimen, was authorized under exceptional circumstances for active immunization for prevention of disease caused by Ebola virus (*Zaire ebolavirus* species) in individuals ≥ 1 year of age [27].

To date, no consistent pattern of obvious impact of baseline Ad26 neutralizing antibodies on immune responses elicited by Ad26-based vaccines has been observed. Data obtained with Janssen's Ad26-based Zika-, HIV-, and COVID-19 vaccine candidates demonstrate the ability to increase the immune response elicited by the first dose with subsequent doses of the same Ad26-based vaccine [18, 19, 23, 28-30]. In addition, data from the Ad26-based Zika vaccine candidate and from the respiratory syncytial virus (RSV) vaccine candidate development programs demonstrate the ability of Ad26-based vaccines to induce a durable immune response up to at least 1 year and 2 years post-vaccination, respectively [29].

3.1.2 Mechanism of Action

After IM administration of Ad26.COV2.S, binding of the Ad26 vector to cellular receptors is mediated by fibers on the Ad26 capsid. After transduction of the cell, episomal vector DNA drives cellular production of the transgene encoded S protein. The S protein is then expressed on the cell membrane where it is sensed by the host immune system, resulting in humoral and cellular immune responses directed against the SARS-CoV-2 S protein.

SARS-CoV-2 infection starts through an interaction of the viral S protein on the surface of the virus with the ACE2 receptor on the surface of host cells. Vaccine elicited neutralizing antibodies may block S protein binding to the ACE2 receptor, thereby inhibiting viral entry into host cells, while other vaccine elicited S specific antibodies may mediate cellular effector mechanisms via their crystallizable fragment (Fc) tail, leading to clearance of SARS-CoV-2 and virus infected cells. Cellular immune responses involve both the CD4+ and CD8+ T-cell compartment. The CD4+ T helper cell responses are predominantly of the Th1-phenotype, supporting production of immunoglobulins and maturation of B cells. CD8+ T-cell immune responses could contribute to

protection from disease by clearing SARS-CoV-2 infected cells via killing of virus-infected cells. Finally, eliciting a strong memory B- and T-cell response could drive a durable protection.

3.1.3 Vaccine Candidate Selection

The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate vaccines against SARS-CoV (2003 outbreak) and SARS-CoV-2, and the common conclusion is that the viral S protein is the only significant target for neutralizing antibodies, while it also contains a significant number of T cell epitopes [31-44]. These findings have been confirmed by human efficacy studies with SARS-CoV-2 vaccines targeting the S protein, and these vaccines have now been shown to be highly efficacious in humans, validating the choice of this protein as target antigen [45, 46].

Prior to selection of Ad26.COV2.S for clinical development, Janssen evaluated 12 S protein designs and 7 different Ad26-based COVID-19 vaccine candidates in vitro and in vivo with design elements previously shown to be successful for other coronavirus S protein-based vaccines, eg, prefusion-stabilizing substitutions and heterologous signal peptides [47-50]. Some of these modifications were shown to increase the induction of neutralizing antibodies compared with wild-type S protein and also showed increase in protective efficacy in nonclinical studies [49-51]. Ad26.COV2.S encodes a full-length, membrane-bound S protein derived from a SARS-CoV-2 clinical isolate [49], with 2 amino acid changes in the S1/S2 junction that knock out the furin cleavage site, and 2 proline substitutions in the hinge region.

3.2 Ad26.COV2.S Dose Selection Rationale

The proposed vaccine regimen is a single immunization with Ad26.COV2.S at a dose level of 5×10^{10} vp, as investigated in the Phase 3 study (COV3001). (See Section 6 for details regarding clinical immunogenicity.)

The dose levels of Ad26.COV2.S that were assessed in the Phase 1/2a study COV1001 (5×10^{10} vp and 1×10^{11} vp) are based on experience with other Ad26-vectored vaccines developed by Janssen that were administered to adults in clinical studies. These two dose levels have shown to be well tolerated and induce a durable immune response in Ad26-based vaccine programs. The selected doses in Phase 1/2a study COV1001 have been evaluated for safety and immunogenicity to assess which regimen would be best suited to address the pandemic or for routine use. The interim analysis, including immunogenicity data from 28 days after one dose in 375 participants ≥ 18 to ≤ 55 years of age and available data in participants ≥ 65 years of age in study COV1001, demonstrated that a single dose of Ad26.COV2.S at 5×10^{10} vp and 1×10^{11} vp induced humoral and cellular responses with high and comparable responder rates. Immunogenicity and clinical efficacy data of the 2-dose regimens will be forthcoming.

In addition, both dose levels had a favorable safety profile, with no safety concerns identified. The 5×10^{10} vp dose had a more favorable reactogenicity profile in comparison to the 1×10^{11} vp dose in participants 18 through 55 years of age. Solicited local and systemic AEs of Grade 3 or higher were more frequent at the 1×10^{11} vp dose level compared with the 5×10^{10} vp dose level (2% vs 0 Grade 3 solicited local AEs and 18.2% vs 9.2% Grade 3 systemic AEs). A pattern of decrease in

frequency and severity of solicited AEs with increasing age of participants was observed in the active vaccine groups. In participants ≥ 65 years of age, reactogenicity did not increase with the 1×10^{11} vp dose level versus the 5×10^{10} vp dose level.

Based on these results, the Phase 3 study COV3001 was initiated with a single Ad26.COV2.S dose at 5×10^{10} vp. Efficacy after a single-dose vaccination would be an advantage for use in the current pandemic situation.

3.3 Proposed Emergency Use Authorization (EUA) Indication Statement

Ad26.COV2.S is indicated for active immunization for the prevention of COVID-19 in adults ≥ 18 years of age, administered as a single dose IM injection of 5×10^{10} vp.

4 SUPPORTING NONCLINICAL INVESTIGATIONS

4.1 Nonclinical Immunogenicity and Efficacy

A single dose of Ad26.COV2.S induced a rapid onset of SARS-CoV-2 neutralizing and S protein binding antibodies in all species tested (mice, rabbits, Syrian hamsters, and nonhuman primates [NHP, Rhesus macaques]). Vaccination with Ad26.COV2.S consistently induced S protein specific CD4+ T cells which were predominantly of the Th1 phenotype and interferon gamma (IFN- γ) producing CD8+ T cells in mice and NHP.

In Syrian hamsters, single dose regimens of Ad26.COV2.S significantly reduced viral load in the lungs after SARS-CoV-2 challenge compared with mock vaccinated and challenged controls. Immunization of NHP with Ad26.COV2.S at dose levels of 1×10^{11} vp or 5×10^{10} vp prior to challenge with SARS-CoV-2 resulted in undetectable lung viral load in all NHP, and undetectable viral load in nasal swabs in most NHP while all non-vaccinated NHP had a high viremia in lung and nasal swabs after SARS-CoV-2 challenge. Ad26.COV2.S elicited dose-depend SARS-CoV-2-specific binding and neutralizing antibodies levels in Syrian hamsters and NHP that correlated with protection from infection with SARS-CoV-2 [52, 53].

In all Syrian hamsters and NHP vaccinated with Ad26.COV2.S and subsequently challenged with SARS-CoV-2, no increased lung histopathology, infectious viral load, or clinical signs were observed compared with the SARS-CoV-2 infected control group, indicating the absence of any signs of VAERD. These studies included animals immunized with sub-optimal dose levels of Ad26.COV2.S, allowing breakthrough viral replication in the lungs after SARS-CoV-2 challenge, conditions which are hypothesized to contribute to a risk of VAERD [53, 54].

NHP vaccinated with a single dose of 5×10^{10} vp or 1×10^{11} vp Ad26.COV2.S maintained durable antibody responses for 6 months that provided lower respiratory tract protection against SARS-CoV-2 challenge. Almost all vaccinated animals had undetectable lung viral load after challenge 6 months after vaccination, while all challenged control animals showed robust SARS-CoV-2 replication that lasted up to 5 days post infection [53, 55].

4.2 Nonclinical Safety

4.2.1 Biodistribution

The biodistribution profile of the Ad26 vector platform has been evaluated in New Zealand White (NZW) rabbits. The Ad26 vector did not widely distribute following IM administration in the animals. Vector DNA was detected at the site of injection, in draining lymph nodes, and (to a lesser extent) in the spleen. The Ad26 vector showed clearance from these tissues.

4.2.2 Toxicology

In a repeat-dose toxicity and local tolerance study in NZW rabbits, IM administration of Ad26.COV2.S at 1×10^{11} vp/dose on three occasions, with a 14-day interval period, was well tolerated. There were no adverse vaccine-related effects noted.

In a combined embryo-fetal and pre- and post-natal development (EF-PPND) toxicity study, 3 doses of Ad26.COV2.S at 1×10^{11} vp/dose were administered IM in female NZW rabbits during the premating (ie, 7 days prior to mating) and gestation period (ie, Day 6 and Day 20 of gestation). There was no adverse effect of Ad26.COV2.S with respect to fertility, or embryo-fetal and postnatal development.

5 REGULATORY AND CLINICAL DEVELOPMENT OVERVIEW

5.1 Regulatory Overview

Development of Ad26.COVS.2 has been accelerated to address the ongoing SARS-CoV-2 pandemic. The program has been conducted in consultation and collaboration with different external partners throughout the different studies, including COVID-19 Response partnership (formerly called Operation Warp Speed [OWS], which includes the Biomedical Advanced Research and Development Authority [BARDA], the National Institutes of Health [NIH, NIAID], and the COVID-19 Prevention Trials Network [CoVPN]), and the United Kingdom (UK) government. The Phase 3 COV3001 study was designed in accordance with FDA guidance on COVID-19 vaccine development [56].

5.2 Clinical Development Program: Initiated Studies

An overview of the five clinical studies of Ad26.COVS.2 that are included in the EUA application is provided in Table 7.

Table 7: Overview of Initiated/Ongoing Clinical Studies of Ad26.COVS.2

Study Identifier/Phase/Status ^a	Countries	Study Objective(s)	Study Design	Participant Population/Number ^a	Dose/Dosing Regimen
COV1001 Phase 1/2a Enrollment complete	Belgium and the US	To assess the safety and reactogenicity of Ad26.COVS.2 at 2 dose levels	Randomized, double-blind, placebo-controlled, first in human	Healthy adults ≥18 to ≤55 years of age (Cohort 1 and Cohort 2) and adults ≥65 years of age (Cohort 3) in good health with or without stable underlying conditions/ 377 enrolled in Cohort 1a, 271 enrolled in Cohort 2, and 403 in Cohort 3	Ad26.COVS.2 5×10 ¹⁰ vp and 1×10 ¹¹ vp, or placebo, administered IM as a single-dose or 2-dose schedule with a 56-day interval. A booster dose will be evaluated in Cohort 2.
COV1002 Phase 1 Enrollment complete	Japan	To assess the safety and reactogenicity of Ad26.COVS.2 at 2 dose levels	Randomized, double-blind, placebo-controlled	Healthy adults ≥20 to ≤55 years of age and ≥65 years in good health with or without stable underlying conditions/ 125 enrolled per cohort	Ad26.COVS.2 5×10 ¹⁰ vp and 1×10 ¹¹ vp, or placebo, administered IM with a 56-day interval
COV2001 Phase 2a Enrollment ongoing	Germany, Spain, the Netherlands. (Additional countries, [eg, UK, USA, Canada and Argentina] are being considered for adolescents)	To assess safety and reactogenicity and humoral immune response of Ad26.COVS.2 across different dose levels and vaccination intervals	Randomized, double-blind, placebo-controlled	Healthy adults ≥18 to ≤55 years of age, and adults in good or stable health ≥65 years of age/ 584 adults enrolled Planned enrollment of healthy adolescents ≥12 to ≤17 years of age (not started)	Ad26.COVS.2 1×10 ¹¹ vp, 5×10 ¹⁰ vp, 2.5×10 ¹⁰ vp, and 1.25×10 ¹⁰ vp, or placebo, in 1- and 2-dose regimens

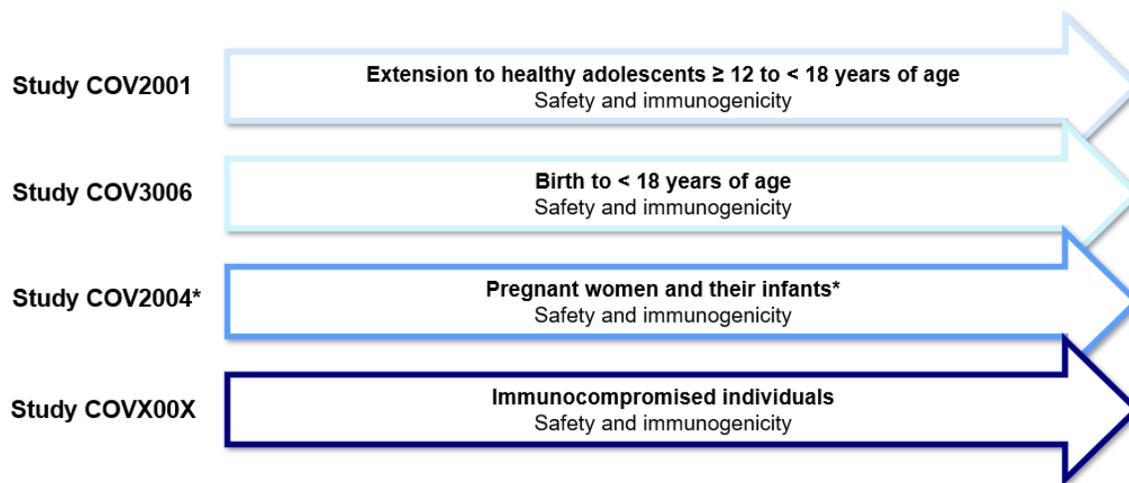
Study Identifier/ Phase/ Status ^a	Countries	Study Objective(s)	Study Design	Participant Population/Number ^a	Dose/Dosing Regimen
COV3001 Phase 3 Enrollment complete	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, US	To demonstrate the efficacy of a single dose of Ad26.COVS.2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19 (with onset at least 14 days and at least 28 days post-vaccination, respectively), as compared to placebo, in SARS-CoV-2 seronegative adults	Randomized, double-blind, placebo-controlled	Adults ≥18 to <60 years of age and ≥60 years of age, with and without relevant comorbidities/ 44,325 randomized, 43,783 vaccinated	Ad26.COVS.2.S 5×10 ¹⁰ vp, or placebo, single dose
COV3009 Phase 3 Enrollment ongoing	Belgium, Brazil (not started), Colombia, France, Germany, Philippines (not started) South Africa, Spain, UK, and US	To demonstrate the efficacy of Ad26.COVS.2.S 2-dose regimen in the prevention of molecularly confirmed, moderate to severe/critical COVID-19 (with onset at least 14 days after the 2nd vaccination), as compared to placebo, in SARS-CoV-2 seronegative adults	Randomized, double-blind, placebo-controlled	Adults ≥18 to <60 years of age and ≥60 years of age, with and without relevant comorbidities/ enrollment ongoing (17,433 randomized)	Ad26.COVS.2.S 5×10 ¹⁰ vp, or placebo, 2-dose regimen with a 56-day interval.

^a based on Janssen’s weekly clinical study status update of 5 February 2021

5.3 Clinical Development Program: Planned Studies

A summary of planned future studies with Ad26.COVS.2.S is provided in Figure 2.

Figure 2: Overview of Planned Clinical Studies of Ad26.COVS.2.S



*Additional data collection through pregnancy exposure registry: occurrence of obstetric, neonatal and infant outcomes

6 CLINICAL IMMUNOGENICITY

Summary

- A single dose of Ad26.COV2.S elicited a wild type SARS-CoV-2 neutralizing antibody (wtVNA), SARS-CoV-2 Spike-binding antibody (S-ELISA) and non-neutralizing functional antibody (as measured by antibody-dependent cellular phagocytosis [ADCP]) response by Day 15 and Day 29 in adult participants ≥ 18 to ≤ 55 years and ≥ 65 years of age.
- Across Phase 1 and 2 studies at Day 29, a SARS-CoV-2 neutralizing antibody response was observed in at least 88% of participants ≥ 18 to ≤ 55 years and at least 93% of participants ≥ 65 years of age.
- Neutralizing and binding antibody responses continued to increase from Day 29 to Day 57 and were maintained to at least Day 85, with very high responder rates across the age groups of ≥ 18 to ≤ 55 and ≥ 65 years of age.
- Neutralizing activity against SARS-CoV-2 variants of the B.1.1.7 lineage (20I/501Y.V1) was reduced compared to the Victoria 1/2020 strain but the decrease in neutralization was smaller at a later timepoint.
- A single dose of Ad26.COV2.S elicited SARS-CoV-2 CD4+ and CD8+ T-cell responses by Day 15 and up to Day 29 in adult participants ≥ 18 to ≤ 55 years and ≥ 65 years of age. In all participants with a CD4+ T-cell response, the response was of the Th1-dominated phenotype.
- In Phase 3, no difference was observed in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S between participants from Brazil, South Africa and the US participants with $>93\%$ responders in the active vaccine groups.
- Similar S binding antibody levels and responder rates were observed across US and Brazil participants irrespective of differences in pre-existing Ad26 neutralizing antibodies at the time of vaccination.

6.1 Assays Used for Immunogenicity Assessments

Assays used for immunogenicity assessments in Ad26.COV2.S clinical studies are summarized in Table 8.

For both wtVNA and S-ELISA assays, a participant response or responder to vaccination was defined as follows:

- If baseline sample value was negative (below the lower limit of quantification) and post vaccination sample value was positive.
- If baseline sample value was positive (above the lower limit of quantification) and post vaccination sample value is ≥ 4 -fold over baseline sample.

For intracellular staining, positivity was based on the Fisher’s exact test for identification of SARS-CoV-2 S protein-specific responses.

Table 8: Immunological Assays Used for Analysis of Immune Responses in the Ad26.COVS.2 Clinical Studies

Assay	Analysis
SARS-CoV-2 Spike (S) enzyme-linked immunosorbent assay (ELISA)	Binding antibodies against SARS-CoV-2 Spike protein
Wild-type SARS-CoV-2 VNA	Neutralizing antibodies against SARS-CoV-2
Antibody-dependent cellular phagocytosis (ADCP)	Binding antibodies against SARS-CoV-2 Spike protein inducing phagocytosis
SARS-CoV-2 Spike ICS	SARS-CoV-2 Spike-specific CD4+ T cells producing IFN- γ , IL-2, IL-4, IL-5, IL-13 and/or CD40L
SARS-CoV-2 Spike IFN- γ and IL-4 ELISpot	SARS-CoV-2 Spike-specific IFN- γ and IL-4 T cell responses
Ad26 VNA	Neutralizing antibodies against Ad26 vector

6.2 Phase 1/2a Study COV1001

6.2.1 Study Design

Study COV1001 is an ongoing, randomized, double-blind, placebo-controlled, first in human Phase 1/2a study, conducted in Belgium and the US, in healthy adults ≥ 18 to ≤ 55 years of age and adults ≥ 65 years of age in good health with and without stable underlying conditions. The primary objective is to assess the safety and reactogenicity of Ad26.COVS.2 at two dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM as a single-dose or 2-dose schedule with a 56-day interval. In addition, immunogenicity of the Ad26.COVS.2 regimens is being assessed.

Here, only the results for the 5×10^{10} vp dose level, that was selected for the Phase 3 studies, are shown. However, immunogenicity of both dose levels was similar in both age groups [30].

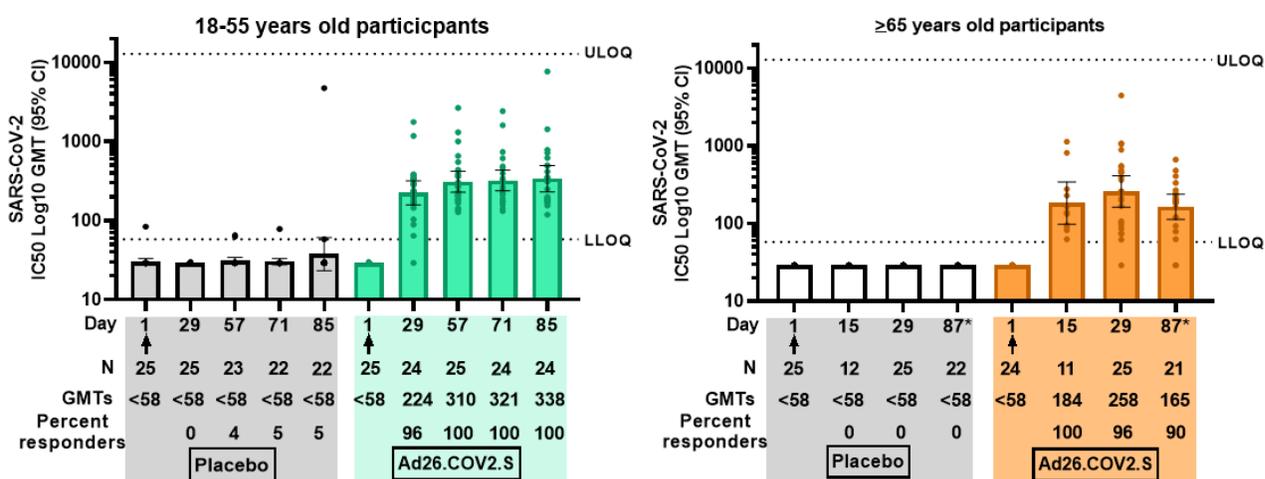
In study COV1001, the initial cohorts enrolling adults aged 18-55 years and ≥ 65 years consisted of 377 and 403 participants, respectively, who were randomized and vaccinated. By the cut-off dates of the analyses presented in this document, all participants in these cohorts had completed the vaccination schedule or had discontinued early. There were no relevant differences in discontinuation rate between the vaccine groups, including placebo. In the cohort of participants aged 18-55 years, the median age (range) at study entry was 34 (18 to 55) years. In the cohort of participants aged ≥ 65 years, the median age (range) at study entry was 69 (65 to 88) years; in this cohort, 8.2% of the participants were > 75 years of age. The median BMI was 24.5 (16.8; 29.9) and 25.7 (16.6; 29.9) kg/mg² among participants aged 18-55 years and ≥ 65 years, respectively. There were no relevant differences in baseline or demographic characteristics between the vaccine groups, including placebo.

A single dose of Ad26.COVS.2 at 5×10^{10} vp was selected as the final regimen for use in the pivotal Phase 3 study COV3001 based on interim data from COV1001 [30].

6.2.2 Humoral Immunogenicity

A single dose of Ad26.COVS elicited a SARS-CoV-2 neutralizing antibody response as measured in a wild type SARS-CoV-2 neutralization assay (wtVNA) by Day 29 (28 days post dose 1) in 96% of participants aged 18-55 years and in 100% and 96% of participants aged ≥ 65 years by Day 15 and Day 29, respectively (Figure 3). Neutralizing antibody levels were maintained in participants aged 18-55 years up to at least Day 85, and up to at least Day 87 for participants aged ≥ 65 years. Responses are in the same range across age groups, and although a slightly lower GMT is observed at Day 87 in participants aged ≥ 65 years, the CIs of the GMT overlap with that of Day 29 responses in participants aged 18 to 55 years.

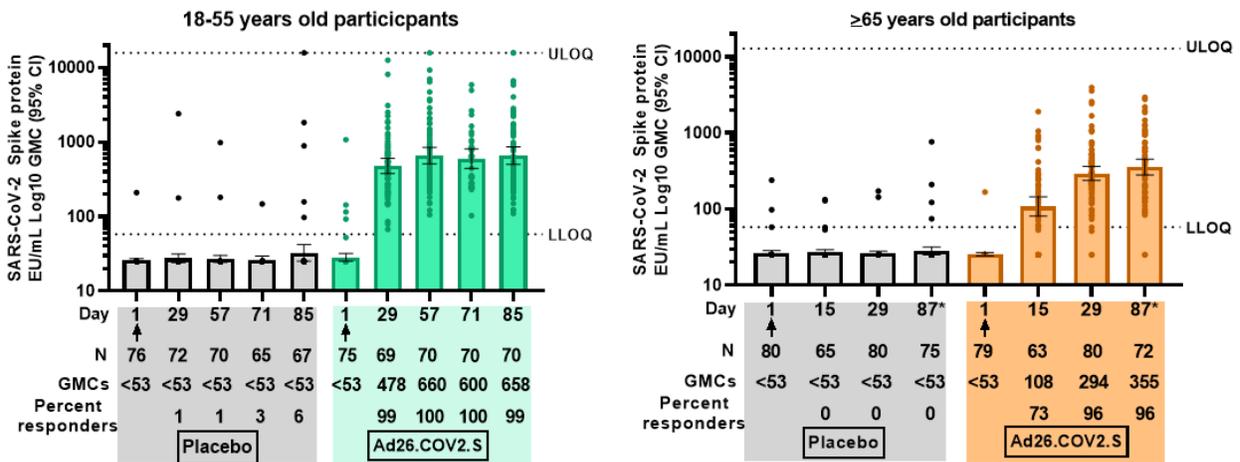
Figure 3: Neutralizing Antibody Titers Induced by a Single Dose of Ad26.COVS at 5×10^{10} vp Dose Level In Participants Aged 18-55 and 65 Years or Older.



NOTE: *For participants ≥ 65 years of age, Day 57 visit was delayed to Day 87 due to overall clinical pause.

Similarly, Spike protein binding antibody responses after one vaccination, as measured by S-ELISA were observed by Day 29 in 99% and 96% of participants aged 18-55 and ≥ 65 years, respectively. The levels of S binding antibodies further increased between Day 29 and Day 57, and were maintained from Day 57 up to at least Day 85 in participants aged 18-55 years (Figure 4). Kinetics of binding antibody responses against the S protein in participants aged ≥ 65 years followed a similar pattern and although observed GMCs are slightly lower in participants aged ≥ 65 years, responses have overlapping ranges.

Figure 4: Spike Protein Binding Antibody Concentrations Induced by a Single Dose of Ad26.COVS.S at 5×10^{10} vp Dose Level in Participants Aged 18-55 and 65 Years or Older



NOTE: * For participants ≥ 65 years of age, Day 57 visit was delayed to Day 87 due to overall clinical pause.

Data on a non-neutralizing antibody functionality, as measured by ADCP, are available from participants aged 18-55 and ≥ 65 years. In both age groups, ADCP activity could be demonstrated as of Day 15 post-vaccination, with a further increase by Day 29, when 79% and $>74\%$ of participants had this activity, respectively (Table 9).

Table 9: Non-neutralizing Antibody Functionality, as Measured by Antibody-dependent Cellular Phagocytosis in Participants Aged 18-55 Years and 65 Years or Older

		18-55-year-old-participants	
Timepoint	Parameters	Ad26.COVS.2.S	Placebo
Baseline	GM of Phagocytic Score (95% CI)	< LOD (< LOD; < LOD)	< LOD (< LOD; < LOD)
	Positive sample n/N (%)	2/75 (3%)	2/76 (3%)
Day 15	GM of Phagocytic Score (95% CI)	13 (< LOD; 16)	< LOD (< LOD; < LOD)
	Positive sample n/N (%)	45/73 (62%)	1/76 (1%)
Day 29	GM of Phagocytic Score (95% CI)	20 (16; 25)	< LOD (< LOD; < LOD)
	Positive sample n/N (%)	57/72 (79%)	3/75 (4%)
		≥ 65-year-old participants	
Timepoint	Parameters	Ad26.COVS.2.S	Placebo
Baseline	GM of Phagocytic Score (95% CI)	< LOD (< LOD; < LOD)	< LOD (< LOD; < LOD)
	Positive sample n/N (%)	1/80 (1%)	1/80 (1%)
Day 15	GM of Phagocytic Score (95% CI)	< LOD (< LOD; < LOD)	< LOD (< LOD; < LOD)
	Positive sample n/N (%)	29/79 (37%)	1/80 (1%)
Day 29	GM of Phagocytic Score (95% CI)	17 (14; 21)	< LOD (< LOD; < LOD)
	Positive sample n/N (%)	59/80 (74%)	1/80 (1%)

New SARS-CoV-2 virus lineages are rapidly developing, including mutations in the virus S protein. Of main concern are the spreading lineages originating from South Africa (lineage B.1.351, variant 20H/501Y.V2), the UK (lineage B.1.1.7, variant 20I/501Y.V1) and Brazil (lineage P.1, variant 20J/501Y.V3) due to mutations that have shown to impact neutralization. To gain some information on potential coverage of Ad26.COVS.2.S elicited immunity for SARS-CoV-2 variants of the B.1.1.7 lineage, neutralizing activity of immune sera from selected participants in COV1001 were tested against the SARS-CoV-2 20I/501Y.V1 variant.

Immune sera from COV1001 participants obtained after a single dose of Ad26.COVS.2.S showed that neutralizing activity against this variant of the B.1.1.7 lineage was approximately 9-fold lower at 28 days and 3.3-fold lower at 70 days compared to neutralization of the reference SARS-CoV-2 Victoria 1/2020 strain. Between 28 and 70 days after vaccination the neutralizing activity against

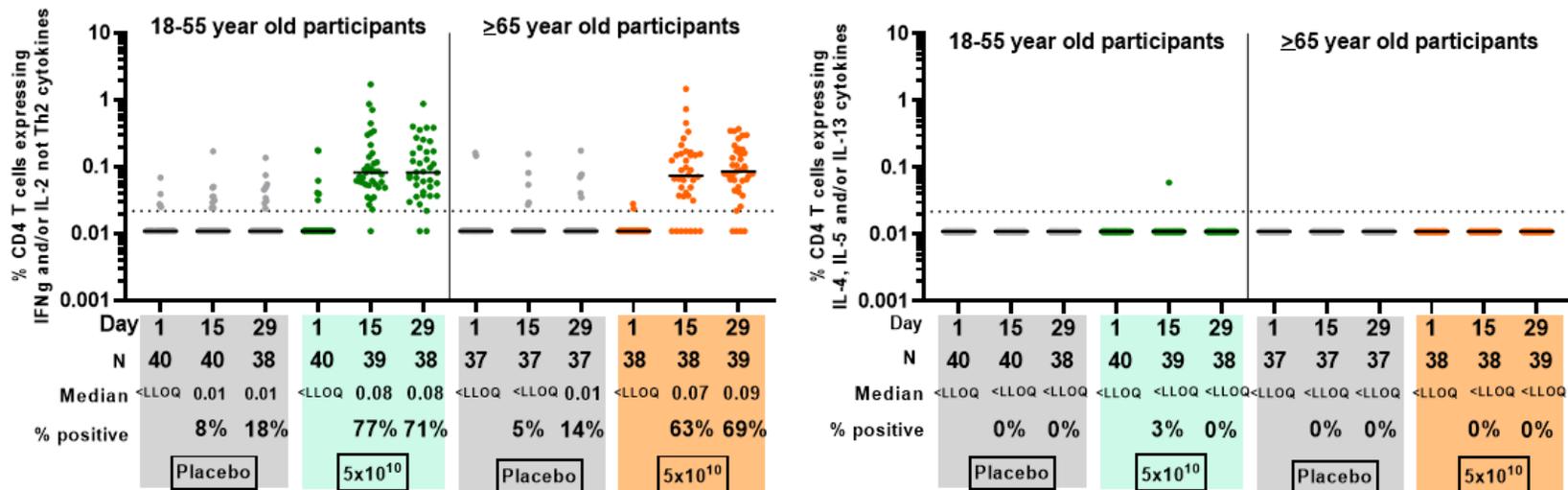
the reference strain also increases. Thus, not only do Ad26.COV2.S elicited antibody titers increase over time, these data also imply maturation of the immune response with improved variant coverage, as demonstrated by the even greater increase in neutralizing activity against the newly emerging SARS-CoV-2 20I/501Y.V1 variant.

6.2.3 Cellular Immunogenicity

A single dose of Ad26.COV2.S elicited S-specific CD4+ and CD8+ T-cell responses.

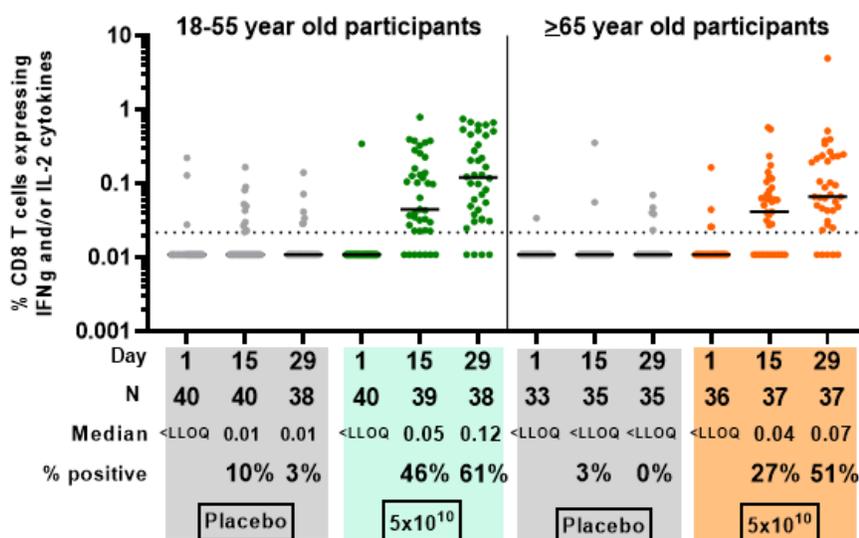
Th1 responses (percentage of CD4+ T cells producing IFN- γ and/or IL-2 but not IL-4, IL-5 and/or IL-13) were detectable as of Day 15 with 77% and 63% in participants aged 18-55 and ≥ 65 years, respectively (Figure 5). Th1 responses were maintained by Day 29, with 71% and 69% responses in both age groups, respectively. Th2 responses (percentage of CD4+ T cells expressing IL-4 and/or IL-5/IL-13 and CD40L) were undetectable at any of the timepoints in either age group (except for one participant whose Th1 response was far greater than their Th2 response). All participants showing a Th1 response post dose 1 vaccination showed a Th1/Th2 ratio of ≥ 1 , indicating a Th1-dominated CD4+ T cell response.

Figure 5: Th1 and Th2 CD4+ Cell Responses Elicited by a Single Dose of Ad26.COVS.S at the 5×10^{10} vp Dose Level in Participants Aged 18-55 Years and 65 Years or Older



CD8+ T cell responses (percentage of CD8+ T cells producing IFN- γ and/or IL-2) were observed as of Day 15, with $\geq 46\%$ and $\geq 27\%$ of participants who had a positive sample in the 18 to 55 and ≥ 65 -year-old groups, respectively (Figure 6). By Day 29, CD8+ T cell responses further increased in both age groups, to 61% and 51% of responders in 18-55 and ≥ 65 -year-old participants, respectively.

Figure 6: CD8+ T Cell Responses Elicited by a Single Dose of Ad26.COVS.S at the 5×10^{10} vp Dose Level in Participants Aged 18-55 Years and 65 Years or Older



These data were confirmed by IFN γ and IL-4 ELISPOT for participants aged 18-55 years (data not shown).

6.3 Phase 1 Study COV1002

Study COV1002 is an ongoing, randomized, double-blind, placebo-controlled Phase 1 study, conducted in Japan, including healthy adults ≥ 20 to ≤ 55 years of age and ≥ 65 years in good health with or without stable underlying conditions. The primary objective is to assess the safety and reactogenicity of Ad26.COVS.S at two dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM with a 56-day interval. In addition, immunogenicity of the Ad26.COVS.S regimens is being assessed.

Ad26.COVS.S elicited SARS-CoV-2 neutralizing antibody responses in 98% of Japanese participants 20-55 years of age, by Day 29 post vaccination. This is consistent with Phase 1/2a COV1001 study results.

6.4 Phase 2a Study COV2001

Study COV2001 is an ongoing, randomized, double-blind, placebo-controlled Phase 2a study, conducted in Germany, Spain, and the Netherlands in healthy adults ≥ 18 to ≤ 55 years of age, and adults in good or stable health ≥ 65 years of age. The primary objectives of this study are to assess safety and reactogenicity and humoral immune response of Ad26.COVS.S across different dose

levels and vaccination intervals. COV2001 will also include a cohort in adolescents ≥ 12 to ≤ 17 years of age that will start enrolling; however, this cohort is out of scope for the current indication and is therefore not included in this briefing document. An overview of the planned studies with Ad26.COV2.S is provided in Figure 2.

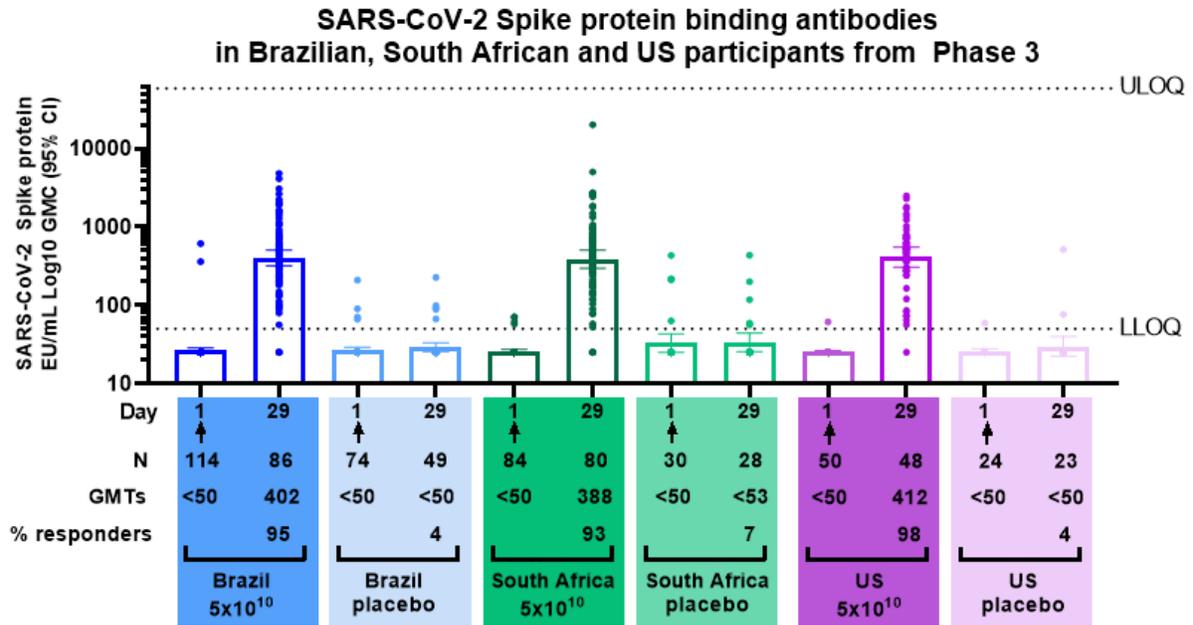
Ad26.COV2.S elicited SARS-CoV-2 neutralizing antibody responses in $>97\%$ of participants aged 18 to 55 years and 93% of participants aged ≥ 65 years, by Day 29 post-vaccination. These results are in line with Phase 1/2a study COV1001 and Phase 1 study COV1002 results.

6.5 Phase 3 Study COV3001 Interim Immunogenicity Results

During the course of study COV3001, it became clear from epidemiological data that viral variants were circulating in some of the countries participating in the study. As an increase in SARS-CoV-2 infection rate was observed in several countries including Brazil and South Africa, it raised concerns that regional differences in VE would be observed at the time of the primary analysis for assessment of Ad26.COV2.S efficacy. Therefore, in addition to planned immunogenicity assessments, Janssen decided to evaluate Ad26.COV2.S immunogenicity by measuring S-specific binding antibodies (by S-ELISA) at Day 1 and Day 29 post-vaccination in participants in Brazilian, South African and US sites. In total, among available samples from Brazil, US, and South Africa, samples from 380 participants (252 Ad26.COV2.S and 128 placebo) were randomly selected and analyzed (118 were from South African sites, 188 from Brazilian sites, and 74 from US sites). For these participants, age was equally distributed between 18-59 and ≥ 60 years and based on the PPI (see Section 7.1.1.6.2).

Overall, no differences were observed in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S between participants from Brazil, South Africa, and the US with $>93\%$ responders in the active vaccine groups (Figure 7). Ad26 seropositive status at baseline was assessed for participants in Brazil and the US. Among the Brazilian participants, 23/27 (85.2%) participants with detectable Ad26 neutralizing antibodies at baseline, and 59/59 (100%) participants with no detectable Ad26 neutralizing antibodies at baseline were vaccine responders as measured by S-ELISA at Day 29. Similar S binding antibody levels and responder rates were observed across US and Brazil participants, irrespective of differences in pre-existing Ad26 neutralizing antibodies at the time of vaccination. GMCs and responder rates across countries were similar to Phase 1/2a study COV1001 data.

Figure 7: Spike Protein Binding Antibody Concentrations Elicited by a Single Dose of Ad26.COVID.S at 5×10^{10} vp Dose Level in Participants >18 Years of Age from Brazil, South Africa and the US



7 CLINICAL EFFICACY

Summary

- Study COV3001 is a multi-country study with a good representation in terms of age, race, ethnicity, and sex, which occurred at a time when the incidence of SARS-CoV-2 was very high and new variants of the virus were emerging.
- Both co-primary endpoints were met. A single dose of 5×10^{10} vp Ad26.COV2.S protects against moderate to severe/critical COVID-19 in adults ≥ 18 years of age with a VE (adjusted 95% CI) of 66.9% (59.03; 73.40) at least 14 days after vaccination and 66.1% (55.01; 74.80) at least 28 days after vaccination. Consistent efficacy is shown across age, race, and ethnicity groups. (based on cases with a positive PCR by central laboratory)
- VE (adjusted 95% CI) against severe/critical COVID-19 at least 14 days after vaccination was 76.7% (54.56; 89.09) and increased to 85.4% (54.15; 96.90) at least 28 days after vaccination, which was consistently high across age groups, regions, and countries. (based on cases with a positive PCR by central laboratory)
- Ad26.COV2.S is effective against moderate to severe/critical COVID-19 caused by newly emerging strains. At least 14 days after vaccination, the VE (95% CI) was 74.4% (65.0; 81.6) in the US, 66.2% (51.0; 77.1) in Brazil, and 52.0% (30.3; 67.4) in South Africa. At least 28 days after vaccination, the VE (95% CI) was 72.0% (58.2, 81.7) in the US, 68.1% (48.8, 80.7) in Brazil, and 64.0% (41.2, 78.7) in South Africa. (based on cases with a positive PCR from any source, regardless of central confirmation)
- VE (95% CI) against COVID-19 requiring medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, ECMO) was 85.8% (38.1; 98.4) at least 14 days after vaccination and 100.0% (31.11; 100.0) at least 28 days after vaccination. (based on cases with a positive PCR from any source, regardless of central confirmation)
- There were no COVID-19-related deaths reported in the Ad26.COV2.S group compared to 5 reported in the placebo group.
- Preliminary data, based on a limited number of Day 71 results, suggest a vaccine effect against asymptomatic infection. This finding needs to be further investigated with additional data.
- The onset of efficacy against moderate to severe/critical COVID-19 began 14 days after vaccination and against severe/critical COVID-19 7 days after vaccination. Efficacy increased through Day 56 after vaccination, especially for severe/critical COVID-19, with 1 severe/critical cases after Day 42 in the Ad26.COV2.S group (Day 48) and 13 cases in the placebo group. This finding is consistent with available immunogenicity results from Phase 1/2a, which show that, following a single dose of Ad26.COV2.S, neutralizing and binding antibody titers were detected as of 14 days after vaccination and increased until 56 days after vaccination with no indication of significant waning up to 84 days after vaccination.
- Participants with moderate COVID-19 in the Ad26.COV2.S group experienced fewer and less severe symptoms than in the placebo group.

7.1 Phase 3 Study COV3001 (ENSEMBLE) – Single Dose Ad26.COVS.2.S

7.1.1 Study Design

7.1.1.1 Overall Design

Study COV3001 is an ongoing randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy, safety, and immunogenicity of a single dose of Ad26.COVS.2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. Study COV3001 comprises participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. The study was conducted in 8 countries on three continents: Argentina, Brazil, Chile, Columbia, Mexico, Peru, the US, South Africa.

The overall design of study COV3001 is illustrated in Figure 8 and scheduled visits and assessments are shown in Figure 9. Participants were randomized in parallel in a 1:1 ratio to receive a single IM injection of either Ad26.COVS.2.S at a dose level of 5×10^{10} vp or placebo.

Figure 8: Phase 3 Study COV3001: Study Design

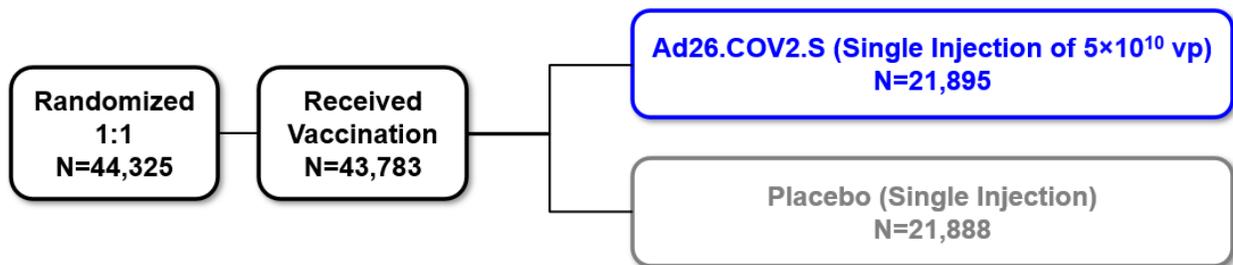
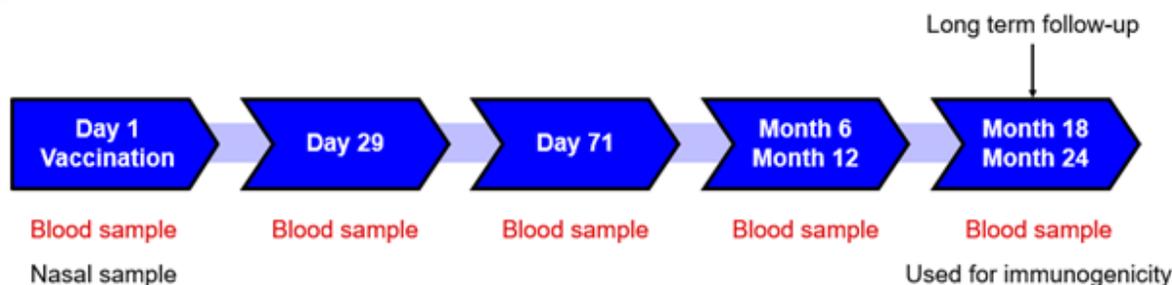


Figure 9: Phase 3 Study COV3001: Scheduled Visits and Assessments



- COVID-19 surveillance throughout via electronic questionnaire, prompts 2x per week for first year after vaccination, 1x per 2 weeks thereafter
- Safety Subset (N = 6,736) to collect reactogenicity signs and symptoms daily for 7 days post vaccination, unsolicited AEs through 28 days
- Medically-attended AEs (MAAEs) captured for first 6 months, SAEs, MAAEs leading to discontinuation for duration of study
- Immunogenicity used for correlates of protection analysis

Note: The safety subset includes participants who provide data on solicited AEs (collected from the day of vaccination until 7 days afterwards) and unsolicited AEs (collected from the day of vaccination until 28 days afterwards).

The study enrolled adults in two age categories: ≥ 18 to < 60 years of age (Stage 1) and ≥ 60 years of age (Stage 2). Both stages were enrolled in parallel. In both age categories, enrollment started with adults without comorbidities that are associated with increased risk of progression to severe/critical COVID-19 (Stages 1a and 2a). After a safety review by the Data Safety Monitoring Board, adults with comorbidities that are associated with increased risk of progression to severe/critical COVID-19 were also eligible to participate (Stages 1b and 2b).

Efforts were made to also ensure good representation in terms of race, ethnicity, and sex. The target for inclusion of participants ≥ 60 years of age was to reach a minimum of approximately 30% of the total study population. However, due to the phased approach of enrollment with the later stage expanding to an older population with comorbidities, exposures in adults ≥ 60 years of age with comorbidities were less than the early recruited cohorts.

7.1.1.2 *Enrollment Criteria*

Adults aged ≥ 18 to < 60 years and adults aged ≥ 60 years, in good or stable health were eligible for inclusion in Stages 1a and 2a, respectively. Adults aged ≥ 18 to < 60 years and adults aged ≥ 60 years with and without stable and well-controlled comorbidities that are associated with an increased risk of progression to severe/critical COVID-19 were eligible for inclusion in Stages 1b and 2b, respectively. Participants who had previously received a coronavirus vaccine and participants with abnormal function of the immune system were ineligible.

If of childbearing potential, participants agreed to practice an acceptable effective method of contraception and agreed to remain on such a method of contraception from providing consent until 3 months after administration of study vaccine. All participants of childbearing potential had

to have had a negative highly sensitive urine pregnancy test at screening and on the day of (and prior to) study vaccine administration.

Participants were ineligible if they had known or suspected allergies or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients.

A full list of enrollment criteria is presented in Appendix 12.1.

7.1.1.3 Independent Review of Severe/Critical COVID-19

A blinded Clinical Severity Adjudication Committee was established to evaluate reported COVID-19 cases for assessment of severe/critical COVID-19. All moderate cases with 3 or more signs and/or symptoms were adjudicated to determine if they met the Protocol definition of severe/critical. All cases were adjudicated individually by a pulmonologist and an infectious diseases specialist and if agreement could not be reached a third committee member would adjudicate the case. Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive.

7.1.1.4 Endpoints

In the initial COV3001 protocol, the primary endpoint was defined as the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 14 days post-vaccination. A co-primary endpoint was added later through an amendment to the protocol, counting COVID-19 cases from 28 days post-vaccination, in addition to from 14 days post-vaccination. This will allow for formal testing and reporting of the primary endpoint counting cases from 28 days post-vaccination as an additional condition for success along with the 14 days post-vaccination endpoint results.

Co-primary endpoints:

- First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 14 days post-vaccination (Day 15)
- First occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days post-vaccination (Day 29)

Separate analyses of the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 14 days and at least 28 days post-vaccination, were conducted by age, sex, race/ethnicity, and comorbidities.

Key secondary endpoints include:

- Vaccine efficacy against severe/critical COVID-19
- Vaccine efficacy against COVID-19 requiring medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, ECMO)
- Vaccine efficacy against all symptomatic COVID-19
- Vaccine impact on asymptomatic or undetected COVID-19 infections

- Effect of the vaccine on SARS-CoV-2 viral load
- Vaccine efficacy against US FDA harmonized definition COVID-19 cases
- All endpoints were repeated with onset one day after vaccination
- All endpoints were evaluated regardless of baseline serostatus

Tertiary endpoints include:

- Vaccine impact on symptom severity
- Vaccine efficacy in subgroups

A supplementary analysis was done, including all cases with a positive PCR from any source, regardless of central confirmation.

Due to the high COVID-19 incidence rate during the conduct of the study and the time it takes logistically to have a positive PCR test confirmed by the central laboratory, it was not possible to complete the confirmation process for all cases by the central laboratory by the time of the primary analysis. This resulted in two data sets:

- a data set of centrally confirmed COVID-19 cases (464 primary endpoint cases)
- non-centrally confirmed: a data set including all COVID-19 cases with a positive PCR from any source (local laboratory, central laboratory, Covance, or external to the study), regardless of central confirmation (682 primary endpoint cases)

For the initial diagnosis of SARS-CoV-2 infection, FDA-approved PCR tests were used, irrespective of whether the test was performed locally in the study or centrally.

Differences in VE estimates based on both data sets were <1% and had similar CIs. Among those cases that have completed the central confirmation process, a high concordance was observed (90.3%). For subgroup analyses, COVID-19 requiring medical intervention, and COVID-19 related deaths, the data set including non-centrally confirmed cases was used to increase the robustness of conclusions. The primary analysis included centrally confirmed cases only.

7.1.1.5 Case Definitions

7.1.1.5.1 Case Definition for Moderate COVID-19

The case definition for moderate COVID-19 was the following:

- A SARS-CoV-2 positive reverse-transcriptase polymerase chain reaction (RT-PCR) or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample

AND at any time during the course of observation:

Any 1 of the following new or worsening signs or symptoms:

- Respiratory rate ≥ 20 breaths/minute
- Abnormal saturation of oxygen (SpO_2) but still $>93\%$ on room air at sea level*
- Clinical or radiologic evidence of pneumonia
- Radiologic evidence of deep vein thrombosis (DVT)
- Shortness of breath or difficulty breathing

OR

Any 2 of the following new or worsening signs or symptoms:

- Fever ($\geq 38.0^\circ C$ or $\geq 100.4^\circ F$)
- Heart rate ≥ 90 beats/minute
- Shaking chills or rigors
- Sore throat
- Cough
- Malaise as evidenced by one or more of the following**:
 - Loss of appetite
 - Generally unwell
 - Fatigue
 - Physical weakness
- Headache
- Muscle pain (myalgia)
- Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)**
- New or changing olfactory or taste disorders
- Red or bruised looking feet or toes

* SpO_2 criteria were adjusted according to altitude per the investigator judgement.

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

7.1.1.5.2 Case Definition for Severe/Critical COVID-19

The case definition for severe/critical COVID-19 was the following:

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

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

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths/minute, heart rate ≥ 125 beats/minute, oxygen saturation (SpO_2) $\leq 93\%$ on room air at sea level*, or partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg)

* SpO_2 criteria were adjusted according to altitude per the investigator judgement

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

- Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to the ICU
- Death

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

All cases meeting the moderate case definition and that include >3 signs and/or symptoms from the list of signs and symptoms are evaluated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive.

7.1.1.5.3 Case Definition for Mild COVID-19

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

AND at any time during the course of observation:

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

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

7.1.1.5.4 US FDA Harmonized Case Definition for COVID-19

If a participant presented with symptoms as those listed by the US FDA harmonized case definition [57], the investigator (or designated medically trained clinician) assessed if these were suggestive of COVID-19:

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

AND

- COVID-19 symptoms consistent with those defined by the US FDA harmonized case definition at the time of finalization of the COV3001 protocol: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.

7.1.1.5.5 Case Definition for Asymptomatic or Undetected COVID-19

If a participant did not fulfill the criteria for suspected COVID-19 based on signs and symptoms:

AND

- had a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample;

OR

- developed a positive serology (non-S protein) test.

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

7.1.1.6 Statistical Analyses

7.1.1.6.1 Sample Size Determination

The sample size was driven by the total number of cases needed to be accrued to reject the null hypothesis. The study target number of events was determined using the following assumptions:

- VE for molecularly confirmed, moderate to severe/critical SARS-CoV-2 infection of 60%.
- Approximately 90% power to reject a null hypothesis of $H_0: VE \leq 30\%$.
- Type 1 error rate $\alpha=2.5\%$ (1-sided) to evaluate VE of the vaccine regimen (employing the truncated sequential probability ratio test [SPRT] to perform a fully sequential design analysis).
- Randomization ratio of 1:1 for active versus placebo.

Under the above assumptions, the total target number of events to compare the active vaccine versus placebo was determined to be 154.

If the primary hypothesis testing was successful for both co-primary endpoints, secondary objectives were to be evaluated against a null hypothesis employing a lower limit $VE > 0\%$.

The evolving epidemiological situation of COVID-19 called for a revision of the sample size. Since the incidence of moderate to severe/critical COVID-19 was significantly higher than assumed at the time of protocol planning, the sample size was reduced from 60,000 to approximately 40,000.

7.1.1.6.2 Analysis Populations

In all populations, participants were analyzed according to the vaccine received. For purposes of analysis, the following populations are defined:

- Full Analysis Set (FAS): All randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment. Analyses of safety was performed on the FAS.
- Safety Subset: Subset of the FAS for the analysis of solicited and unsolicited AEs.
- Per-Protocol Efficacy (PP) population: Participants in the FAS who receive study vaccine and were seronegative at the time of vaccination (Day 1). In addition, participants with

positive PCR at baseline as well as participants with major protocol deviations judged to possibly impact the efficacy of the vaccine were excluded from the PP population. The primary analysis of VE was based on the PP population.

- Per Protocol At Risk set: Day 14: includes all participants in the PP population but excludes participants with a positive PCR test result between vaccination (Day 1) and Day 14; Day 28: includes all participants in the PP population but excludes participants with a positive PCR test result between vaccination (Day 1) and Day 28.
- Per-protocol Immunogenicity (PPI) population: All randomized and vaccinated participants, including those who are part of the Immunogenicity Subset and for whom immunogenicity data are available, excluding participants with major protocol deviations expected to impact the immunogenicity outcomes.

7.1.1.6.3 Efficacy Analysis

For both co-primary endpoints, magnitude of the difference between Ad26.COV2.S and placebo was assessed at a 2.5% one-sided significance level.

A successful primary efficacy conclusion required:

1. Establishing the hypothesis $H_1: VE > 30\%$ for each co-primary endpoint and a VE point estimate $\geq 50\%$ for each co-primary endpoint. For both co-primary endpoints, the following hypothesis was tested: $H_0: VE \leq 30\%$ versus $H_1: VE > 30\%$ and each hypothesis was evaluated at a 2.5% one-sided significance level;

AND

2. A favorable split vaccine:placebo for the subset of primary endpoints meeting the severe/critical COVID-19 case definition (expressed as a VE point estimate against severe/critical COVID-19 molecularly confirmed endpoints $\geq 50\%$) and a minimum of 5 events in the placebo group. This requirement needed to be met for severe/critical events with onset at least 14 days after vaccination and for severe/critical events with onset at least 28 days after vaccination.

Both conditions 1 and 2 simultaneously had to be met for both co-primary endpoints at the same calendar timepoint.

To evaluate the primary null hypotheses: $H_0: VE \leq 30\%$ versus $H_1: VE > 30\%$ for the co-primary endpoints, the truncated SPRT was used based on accumulating event data for each co-primary endpoint. This boundary was set up using the fully sequential design and was derived in such a way to have approximately 90% power to detect a $VE=60\%$ using a one-sided $\alpha=0.025$ against $H_0: VE \leq 30\%$, starting at 20 events up to 154 events.

Exact Poisson regression was used to estimate the VE and associated CI taking into account the follow-up time. The follow-up time for each participant is defined as time since vaccination until onset of a COVID-19 episode or the last available study measurement (22 January 2021). If <6 cases were observed for an endpoint, the VE is not displayed.

Primary efficacy and safety analyses were performed once the required 2-month median follow-up was reached (defined as a minimum of 8 weeks of median follow-up post vaccination, reached on 22 January 2021).

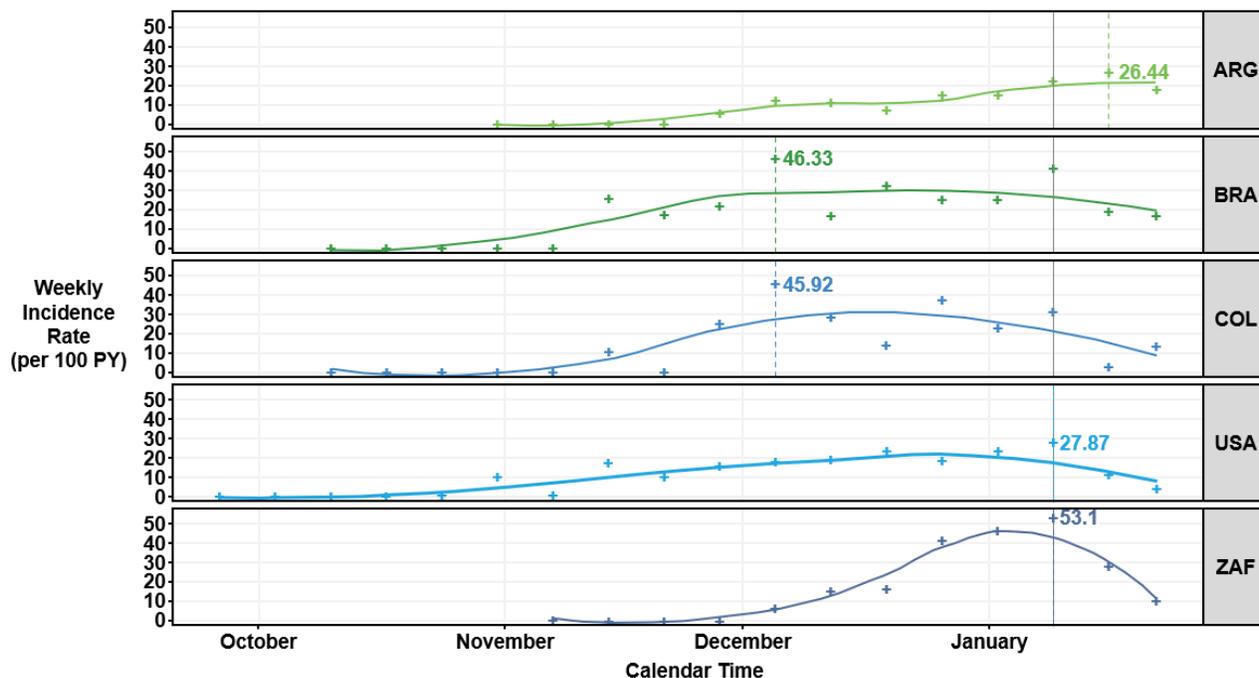
7.1.2 Epidemiological Setting

The Phase 3 efficacy study COV3001 is being conducted in a period of very high SARS-CoV-2 transmission, and during a time when new variants of the virus are emerging. COV3001 started in the US on 21 September 2020 and then gradually included multiple countries. In the last quarter of 2020, the incidence of SARS-CoV-2 infections increased significantly across the globe, including in the countries where the study was being conducted (Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the US).

The weekly annualized incidence rate of COVID-19 in seronegative placebo participants over time, including the peak of infection, is shown in Figure 10 by country (including those with a substantial number of participants/ molecularly confirmed cases). The estimated annualized incidence during the entire course of the study was 19.8% (based on cases with a positive PCR from any source, regardless of central confirmation). There was a peak incidence rate in South Africa of >50%.

In addition, prior to the primary analysis, the emergence of new SARS-CoV-2 variants in some countries where the study was being conducted became apparent (see Section 7.1.7.1 for additional discussion of the new variants).

Figure 10: Peak Weekly COVID-19 Annualized Incidence in the Placebo Group, Seronegative Participants, of Study COV3001 (FAS)



Note: Annualized incidence expressed as # cases/100 person-years. Dashed vertical line: highest peak weekly incidence; solid vertical Line: 14 days prior to database cut-off.

Includes cases with a positive PCR from any source, regardless of central confirmation.

Due to the low number of molecularly confirmed cases/participants in the Ad26.COVS.2.S group and placebo group in Chile (1/531 each) Peru (0/571 each) and Mexico 1/206 and 0/205, respectively) there is no graphical presentation for these countries.

The apparent observed decrease in COVID-19 incidence depicted above, after 7 January 2021, may be partially due to operational reasons: operational time from local sampling to PCR confirmation in the central laboratory was estimated to be an average of 14 days, with a longer confirmation time in some countries in the Latin America region and South Africa. Therefore, some cases after the database cut-off may be pending.

7.1.3 Participant Disposition

The disposition of participants in study COV3001 is shown in Figure 11. A total of 44,325 participants were randomized and 43,783 were vaccinated (21,895 in the Ad26.COVS.2.S group and 21,888 in the placebo group) and are included in the FAS. The PP set includes 39,321 participants (19,630 in the Ad26.COVS.2.S group and 19,691 in the placebo group).

In the PP set, 130 (0.3%) participants, including 41 (0.2%) participants in the Ad26.COVS.2.S group and 89 (0.5%) participants in the placebo group, discontinued the study prematurely, mainly due to withdrawal of consent (30 [0.2%] participants in the Ad26.COVS.2.S group and 62 [0.3%] participants in the placebo group). At the time of the primary analysis, the median follow-up after vaccination was 58 days, and 21,491 participants in the PP set had at least 2 months (8 weeks) of follow-up.

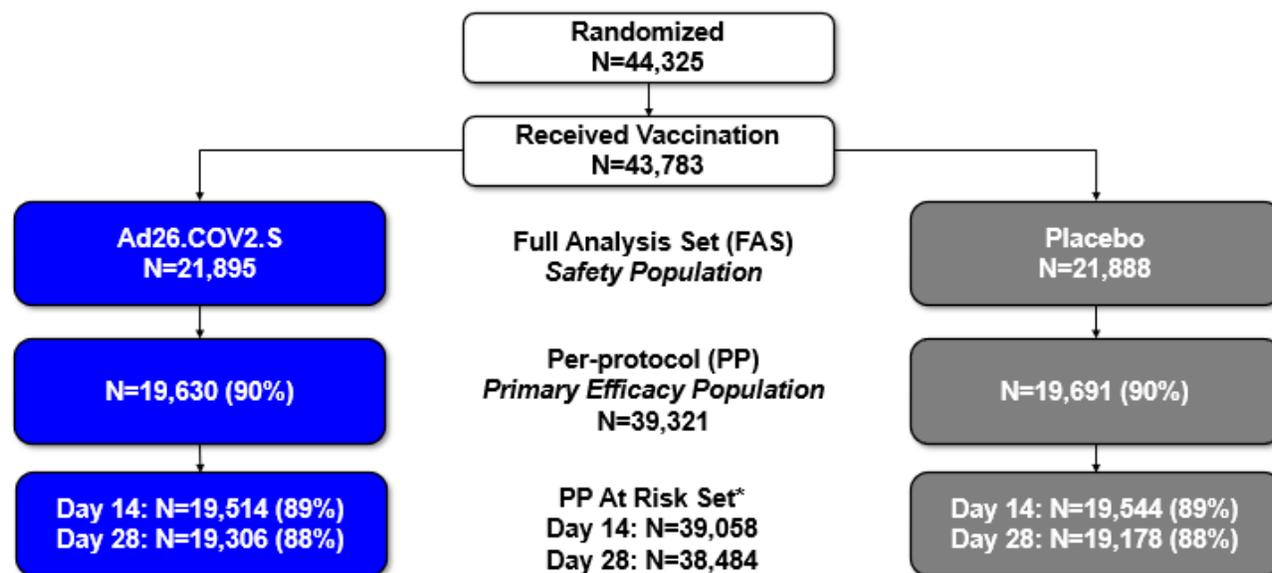
Study participants who became eligible to receive an authorized/licensed COVID-19 vaccine according to local immunization guidelines or recommendation could request to be unblinded per

protocol. All participants who were unblinded for this purpose could remain in the study and were encouraged to continue to be followed, whether they were in the vaccine or control group. Up to the cut-off date of 22 January 2021, a total of 2,257 (5.2%) participants were unblinded (FAS; 1,080 [4.9%] and 1,177 [5.4%] participants in the Ad26.COV2.S and placebo group, respectively) were unblinded. Data collected up to unblinding are included in the analysis described in this document.

Janssen has proposed that, if EUA is granted, a single dose of Ad26.COV2.S will be offered to participants who initially received placebo in Study COV3001, resulting in de facto unblinding of participants and investigators. Additional details on the proposal are provided in Section 7.2.

The At Risk set of the PP population included 39,058 participants at Day 14 (19,514 in the Ad26.COV2.S group and 19,544 in the placebo group) and 38,484 participants at Day 28 (19,306 in the Ad26.COV2.S group and 19,178 in the placebo group).

Figure 11: Disposition of Participants in Study COV3001



*PP At Risk Set: Excluded participants from PP population with positive polymerase chain reaction (PCR) test for SARS-CoV-2 between vaccination and Day 14 or Day 28.

7.1.4 Participant Demographics

No relevant differences in demographics and baseline characteristics were observed between the Ad26.COV2.S group and the placebo group in either the FAS (Table 10) or the subgroup of US participants (Table 11). Randomization was stratified by vaccination unit (site), age and presence/absence of comorbidities that are or might be associated with an increased risk of progression to severe/critical COVID-19. Predefined targets for subgroups were reached with good representation in terms of age, race, ethnicity, and sex. Additional demographic breakdown for age and comorbidities for the FAS and the US subgroup are presented in Appendix 12.2 in Table 20 and Table 21, respectively.

Table 10: Global Baseline Demographics and Comorbidities (Study COV3001)

Full Analysis Set (FAS)	Ad26.COV2.S N=21,895		Placebo N=21,888	
	n	%	n	%
Sex, Female	9820	44.9%	9902	45.2%
Age, years				
Mean (SD)	50.7 (15.1)		50.7 (15.0)	
Age Group				
18-59	14564	66.5%	14547	66.5%
≥60	7331	33.5%	7341	33.5%
≥65	4259	19.5%	4302	19.7%
≥75	809	3.7%	732	3.3%
Country				
Brazil	3644	16.6%	3634	16.6%
South Africa	3286	15.0%	3290	15.0%
Chile	563	2.6%	570	2.6%
United States	9655	44.1%	9647	44.1%
Argentina	1498	6.8%	1498	6.8%
Colombia	2125	9.7%	2123	9.7%
Peru	886	4.0%	885	4.0%
Mexico	238	1.1%	241	1.1%
Race				
American Indian or Alaska Native	2083	9.5%	2060	9.4%
Asian	743	3.4%	687	3.1%
Black or African American	4251	19.4%	4264	19.5%
Native Hawaiian or other Pacific Islander	58	0.3%	48	0.2%
White	12858	58.7%	12838	58.7%
Multiple	1204	5.5%	1245	5.7%
Unknown, not reported	697	3.2%	744	3.4%
Ethnicity				
Hispanic or Latino	9874	45.1%	9963	45.5%
≥1 Comorbidity*	8936	40.8%	8922	40.8%
Obesity	6277	28.7%	6215	28.4%
Hypertension	2225	10.2%	2296	10.5%
Type 2 Diabetes	1600	7.3%	1549	7.3%
Serious heart conditions	497	2.3%	511	2.3%
HIV (positive)	601	2.7%	617	2.8%

*Cut off at ≥2.0% in either group

Table 11: US Baseline Demographics and Comorbidities (Study COV3001)

US Subgroup	Ad26.COV2.S n=9,655		Placebo n=9,647	
	n	%	n	%
Full Analysis Set (FAS)				
Sex, Female	4292	44.5%	4256	44.1%
Age, years				
Mean (SD)	53.0 (14.71)		53.2 (14.68)	
Age Group, years				
18-59	5894	61.0%	5870	60.8%
≥60	3761	39.0%	3777	39.1%
≥65	2299	23.8%	2369	24.6%
≥75	445	4.6%	416	4.3%
Race				
American Indian or Alaska Native	92	1.0%	95	1.0%
Asian	655	6.8%	597	6.2%
Black or African American	1246	12.9%	1264	13.1%
Native Hawaiian or other Pacific Islander	47	0.5%	41	0.4%
White	7104	73.6%	7090	73.5%
Multiple	181	1.9%	179	1.9%
Unknown, not reported	329	3.4%	379	3.9%
Ethnicity				
Hispanic or Latino	1381	14.3%	1454	15.1%
≥1 Comorbidity*	4227	43.8%	4247	44.0%
Obesity	3085	32.0%	3054	31.7%
Hypertension	1139	11.8%	1166	12.1%
Type 2 Diabetes Mellitus	743	7.7%	729	7.6%
Serious heart conditions	291	3.0%	304	3.2%
Asthma	160	1.7%	203	2.1%
HIV (positive)	141	1.5%	153	1.6%

*Cut off at ≥2.0% in either group.

7.1.5 Primary Endpoint Results – Moderate and Severe Disease

7.1.5.1 Co-Primary Efficacy Results

The VE was 66.9% (adjusted 95% CI: 59.03, 73.40) and 66.1% (adjusted 95% CI: 55.01, 74.80) from at least 14 and at least 28 days after vaccination, respectively (Table 12).

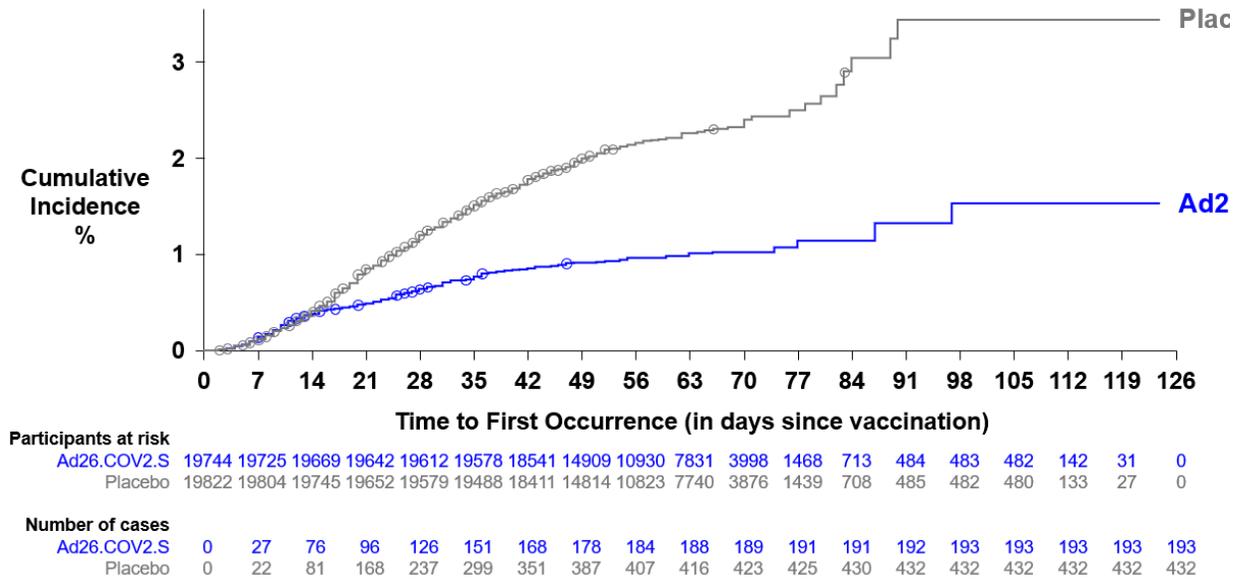
Hypothesis testing was successful for both co-primary endpoints and, thus, the ability of a single dose of Ad26.COV2.S at 5×10^{10} vp to protect against moderate to severe/critical COVID-19 as early as 14 days after vaccination was demonstrated in adults ≥18 years of age, including adults ≥60 years of age.

Table 12: Vaccine Efficacy Against Molecularly Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 Days and at Least 28 Days After Vaccination, Per Protocol Population (Study COV3001)

Vaccine Efficacy Against Molecularly Confirmed Moderate to Severe/Critical COVID-19				
	With Onset at Least 14 Days After Vaccination		With Onset at Least 28 Days After Vaccination	
Per Protocol (PP)	Ad26.COVS.2 N=19,630	Placebo N=19,691	Ad26.COVS.2 N=19,630	Placebo N=19,691
Number of cases, n	116	348	66	193
Person Years	3116.57	3096.12	3102.00	3070.65
Vaccine efficacy (VE) (Adjusted 95% CI)	66.9% (59.03, 73.40)		66.1% (55.01, 74.80)	

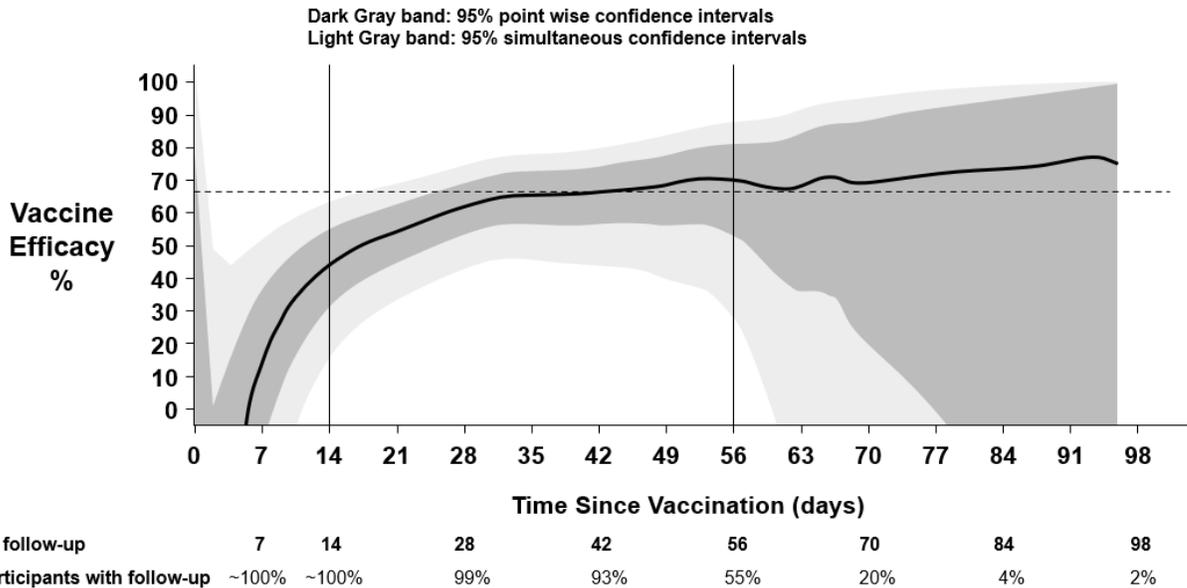
Onset of protection was observed as early as 14 days after vaccination against moderate to severe/critical COVID-19 (Figure 12). The cumulative incidence curves for the first occurrence of moderate to severe/critical COVID-19 begin to separate between the Ad26.COVS.2 and the placebo group around 14 days after vaccination.

Figure 12: Cumulative Incidence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases with Onset at Least 1 Day after Vaccination up to Day 126, Full Analysis Set (Study COV3001)



Note: Severe cases are marked as blue or grey circles on the graphs.

Figure 13: Vaccine Efficacy Over Time for Molecularly Confirmed Moderate to Severe/Critical Cases (FAS)



The graph with the VE over time is generated using the methodology of Gilbert [58] and is estimating the VE as the log hazard ratio over time through smoothing methods. For smoothing, a window of 21 days was used. The VE estimates become difficult to interpret with small numbers of cases. Therefore, the VE estimate over time prior to Day 14 may be unreliable. Furthermore, since the number of participants with follow-up beyond Day 56 significantly decreases, the graphs should be interpreted with caution. This uncertainty is reflected in the width of the CIs around the estimated VE curve beyond that timepoint.

Vaccine efficacy against moderate to severe/critical COVID-19 increased over time through Day 56 (Figure 13). This observation is in line with the Phase 1/2a immunogenicity findings (see Section 6.2), which demonstrated that, following a single dose of Ad26.COVS.2, neutralizing and binding antibody titres are detected as of Day 15 and neutralizing and binding antibody titres increased from Day 29 to Day 57 with no indication of significant waning up to at least Day 85 (last available date). It should be noted that the proportion of participants in COV3001 with follow-up data after Day 57 is currently limited, with only 20% of participants reaching the Day 71 timepoint. Longer and more follow-up data are being collected to determine duration of protection beyond 2 months after vaccination.

7.1.6 Secondary Endpoint Results

Because the co-primary analyses were successful, secondary endpoints were statistically tested with the criterion of a lower limit of the CI to be above 0% according to the prespecified hypothesis testing scheme. Table 1 shows a summary of selected secondary endpoint results, with additional details in Sections 7.1.6.1 to 7.1.6.8.

7.1.6.1 Vaccine Efficacy Against Severe/Critical COVID-19

Vaccine efficacy against molecularly confirmed severe/critical COVID-19 occurring at least 14 days after vaccination was 76.7% (adjusted 95% CI: 54.56, 89.09) and increased to 85.4% (adjusted 95% CI: 54.15, 96.90) as of 28 days after vaccination. There were 14 vs 60 cases of molecularly confirmed severe/critical COVID-19 occurring at least 14 days after vaccination in the Ad26.COVS.2 group vs placebo, respectively, and 5 vs 34 cases of molecularly confirmed severe/critical COVID-19 occurring at least 28 days after vaccination in the Ad26.COVS.2 vs placebo group, respectively. These case splits for severe/critical COVID-19 in the Ad26.COVS.2 vs placebo group virtually eliminate the risk of VAED, consistent with the Th1 skewed immunologic response.

The cumulative incidence of molecularly confirmed severe/critical COVID-19 cases with an onset of at least 1 day after vaccination to Day 126 is displayed in Figure 14 and demonstrates the early onset of protection. The cumulative distribution curves begin to separate between the Ad26.COVS.2 group and the placebo group around 7 days after vaccination. As of Day 42, there is only one molecularly confirmed severe/critical COVID-19 case (Day 48) reported in the Ad26.COVS.2 group and 13 cases in the placebo group, resulting in an estimated VE from Day 42 onwards (calculated post-hoc) of 92.4% (49.62; 99.82). A trend of increasing VE up to Day 56 was observed (Figure 15). It should be noted, however, that follow-up data beyond Day 56 are limited.

Figure 14: Cumulative Incidence of Molecularly Confirmed Severe/Critical COVID-19 Cases with Onset at Least 1 Day after Vaccination up to Day 126, Full Analysis Set (Study COV3001)

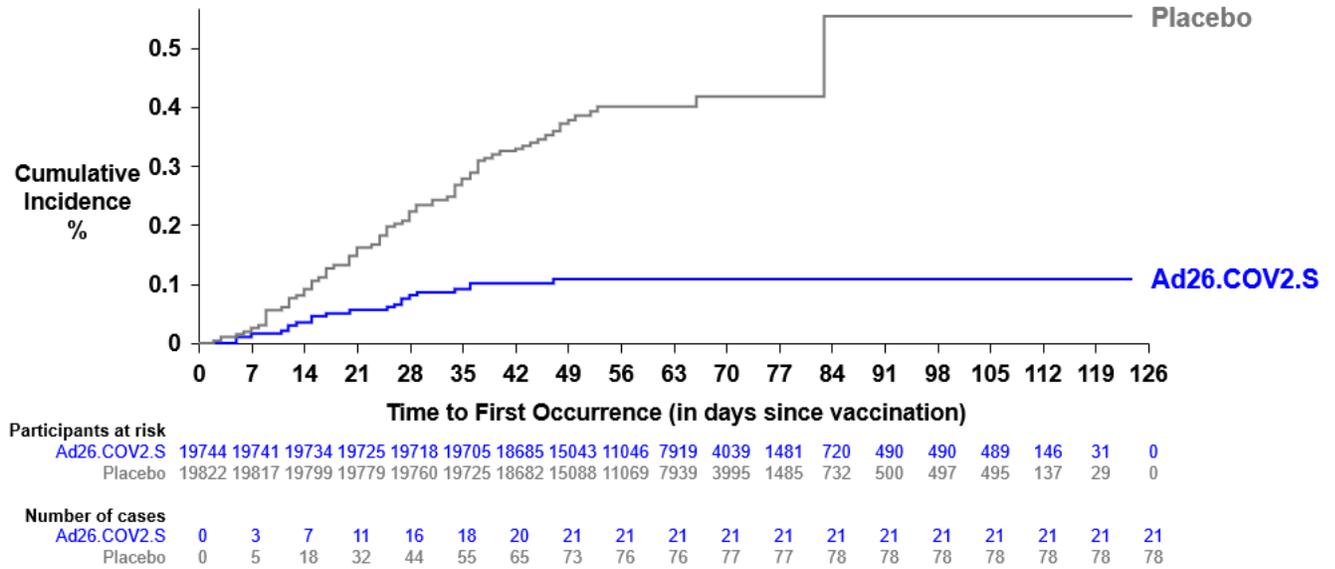
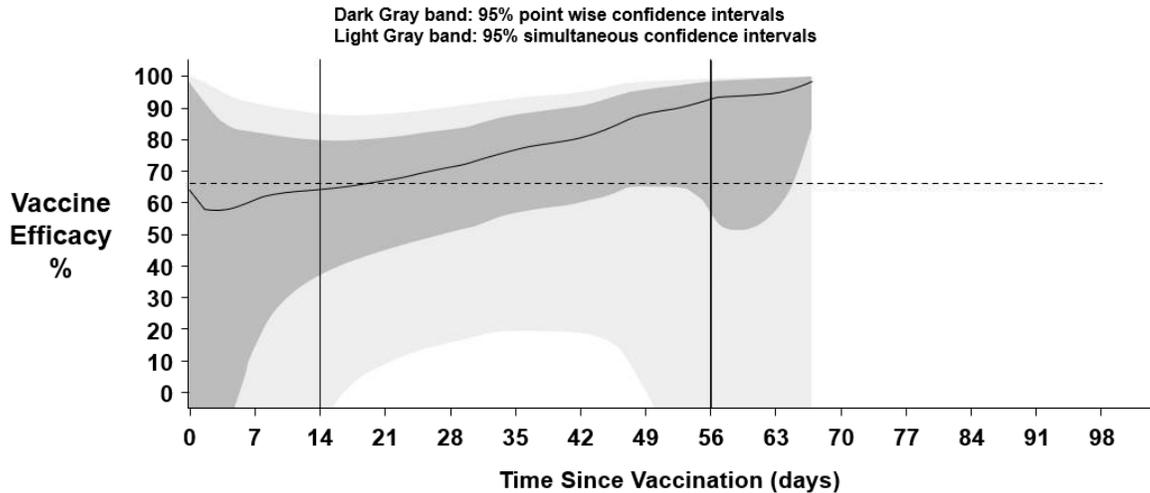


Figure 15: Vaccine Efficacy Over Time for Molecularly Confirmed Severe/Critical Cases (FAS)



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

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

7.1.6.2 *Prevention of COVID-19 Requiring Medical Intervention*

Although the number of reported cases of COVID-19 that required medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, and ECMO linked to objective measures such as decreased oxygenation, X-ray or computerized tomography [CT] findings) was not sufficient to perform inferential testing (ie, <23 as prespecified in the Statistical Analysis Plan [SAP]), data suggest a trend toward an effect of Ad26.COVS.2 in the prevention of COVID-19 requiring medical intervention.

Ad26.COVS.2 was observed to have an impact on COVID-19 requiring medical intervention as determined by the Medical Resource Utilization (MRU) form, completed by the investigator (Table 13).

Table 13: COVID-19 Requiring Medical Intervention

Per Protocol (PP)	Ad26.COVS.2 N=19,630 Cases, n	Placebo N=19,691 Cases, n	VE (95% CI)*
Medical intervention (MRU)^a			
PCR+ by central laboratory^b			
Day >14	2	8	75.0% (-25.3; 97.4)
Day >28	0	5	--
PCR+ from any source^c			
Day >14	2	14	85.8% (38.1; 98.4)
Day >28	0	7	100.0% (31.4; 100.0)

* If fewer than 6 cases observed across groups, no VE/CI is calculated.

^a Medical intervention is defined as hospitalization, ICU admission, mechanical ventilation, ECMO linked to objective measures as decreased oxygenation, X-ray or CT findings, and as reported on the MRU form, completed by the investigator.

^b Analysis based on a data set of centrally confirmed COVID-19 cases.

^c Analysis based on a data set including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation.

At the time of the primary analysis cut-off date, not all MRU Forms were available. Review of SAE forms, which are forwarded sooner following an event than MRU Forms, revealed additional COVID-19 cases associated with hospitalization (see Table 14). These data further support the finding that there may be a substantial effect of Ad26.COVS.2 in the prevention of COVID-19 requiring medical intervention.

Table 14: Hospitalization Associated with COVID-19, Not Included in the MRU Form Analysis

Full Analysis Set (FAS)	N=21,895 Cases, n	N=21,888 Cases, n	VE (95% CI)*
Additional cases of hospitalization identified based on SAE reporting[#]			
Day >1	1	16	--

* If fewer than 6 cases observed across groups, no VE/CI is calculated

[#] At the time of the primary analysis cut-off date, not all MRU Forms were available. Review of SAE forms, which are forwarded sooner, following an event, than MRU Forms

For one participant in the Ad26.COVS.2 group who was hospitalized on Day 36, there was an AE of COVID-19, which started on Day 23, with a PCR+ test result on Day 36.

7.1.6.3 Prevention of COVID-19-Related Death

Data suggest a trend toward an effect of Ad26.COVS.2 in the prevention of COVID-19-related death. Overall, 19 deaths occurred: 3 in the Ad26.COVS.2 group vs 16 in the placebo group. Five of the deaths in the placebo group were confirmed to be COVID-19 associated (WHO classification and positive PCR test), and a 6th COVID-19-associated death occurred in a participant in the placebo group with a positive SARS-CoV-2 RT-PCR test at baseline. All COVID-19-associated deaths occurred in South Africa. None of the deaths in the Ad26.COVS.2 group was confirmed to be COVID-19 associated.

Section 8.4.3.2 provides a more detailed analysis of the deaths that occurred in study COV3001.

7.1.6.4 Vaccine Efficacy Against All Symptomatic COVID-19 (BOD)

Vaccine efficacy (adjusted 95% CI) against all symptomatic molecularly confirmed COVID-19 evaluated through a severity-adjusted score (burden of disease [BOD] endpoint)[59] was 68.1% (60.3, 74.3) as of 14 days after vaccination and 69.0% (56.7, 77.6) as of 28 days after vaccination. The BOD endpoint gives a higher weight to severe infections (severe cases receive a score of 2 and mild or moderate cases a score of 1) and, as such, differentiates vaccines with increased protection against severe infections from placebo.

The efficacy (95% CI) against molecularly confirmed moderate COVID-19 was 64.8% (55.8, 72.2) 14 days after vaccination and 62.0% (48.7, 72.2) 28 days after vaccination. There were too few mild cases reported (4 molecularly confirmed cases and 15 cases regardless of confirmation from the central laboratory with onset at least 14 days after vaccination) to draw meaningful conclusions, which may be due to the broad definition of moderate COVID-19, which captures almost all observed symptomatic COVID-19 disease.

7.1.6.5 Vaccine Impact on Symptom Severity

The impact of Ad26.COVS.2 on the symptom severity in moderate COVID-19 cases was assessed by means of the Symptoms of Infection with Coronavirus-19 (SIC) questionnaire completed by study participants. In addition, the impact of Ad26.COVS.2 on the symptom severity in severe/critical COVID-19 cases was then assessed.

The SIC questionnaire asks the participant if he/she had any of a list of prespecified signs or symptoms during the past 24 hours, and to rate the severity on a 10-point scale.

The total SIC score is lower in participants with confirmed moderate COVID-19 with onset at least 14 days after vaccination in the Ad26.COVS.2 group compared to the placebo group, during the first 11 days and reach a plateau thereafter. With onset at least 28 days after vaccination, the total SIC score is lower in the Ad26.COVS.2 group compared to the placebo during the first 22 days.

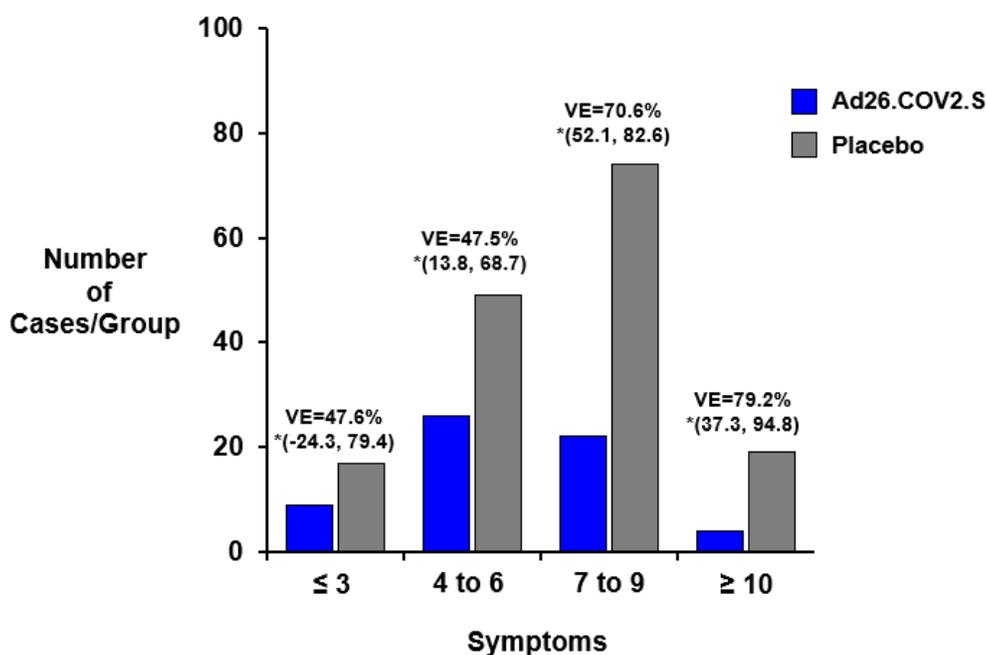
Based on the daily questionnaire, as self-reported by participants during a moderate COVID-19 episode (PCR positive by central laboratory, with onset 28 days after vaccination), the average

total symptom severity score was 1.20 in the vaccine group compared to 1.58 in the placebo group on Day 1 (24% reduction), 0.40 compared to 0.76 on Day 7 (47% reduction) and 0.10 compared to 0.22 on Day 14 (55% reduction)¹.

A post-hoc analysis demonstrated that participants with moderate COVID-19 who received Ad26.COVS.S most frequently reported 4 to 6 symptoms while participants in the placebo group reported 7 to 9 symptoms.

Vaccine efficacy increased with an increasing number of symptoms. The vaccine was more efficacious against moderate COVID-19 with >6 symptoms (>75% and >70%) compared to moderate COVID-19 with ≤6 symptoms (<52% and approximately 47%) with an onset at least 14 days and at least 28 days after vaccination, respectively (Figure 16). The results at least 14 days after vaccination were consistent with the results at least 28 days after vaccination.

Figure 16: Summary of Efficacy of first Occurrence of Moderate COVID-19 with Onset at Least 28 Days After Vaccination by Number of Symptoms; Per Protocol Set (Study VAC31518COV3001)



*95% Confidence Interval

The Y-axis represents the number of cases and the height of the bar represents the number of cases observed in each category

¹ Reductions calculated post-hoc

7.1.6.6 Vaccine Impact on Asymptomatic COVID-19 Infections as Inferred Through Seroconversion

In a preliminary analysis of asymptomatic or undetected COVID-19 infection based on an assessment of (SARS-CoV-2 N IgG) seroconversion in 965 individuals with Day 71 results available, 16 asymptomatic or undetected cases occurred in the placebo group versus 2 cases in the Ad26.COV2.S group resulting in VE of 87.8% (95% CI: 48.27; 98.64).

Seroconversion was defined as a participant who develops a positive serology [non-S protein] test without a SARS-CoV-2 positive RT-PCR result in the period before the positive serology test (ie, this included cases without symptoms and undetected cases i.e., participants with symptoms for whom a SARS-CoV-2 RT PCR test was not performed or was negative).

When a sensitivity analysis was done removing all participants with symptoms at any time since screening prior to the SARS-CoV-2 N IgG positive result (i.e., removing the undetected cases with symptoms), 0 and 12 seroconversions occurred in the Ad26.COV2.S and placebo group, respectively (VE [95% CI]: 100.0% [65.06; 100.00]). Based on 16 cases and 479 participants in the serology at risk set in the placebo group, the seroconversion attack rate equals 3.3%.

As these findings are based on only a limited subset of Day 71 results (as only a limited number of participants had reached the Day 71 timepoint), these findings are preliminary and further follow up is needed to assess whether this finding is confirmed with a larger dataset.

7.1.6.7 Effect of Vaccine on SARS-CoV-2 Viral Load

Exploratory quantification of the SARS-CoV-2 viral load was performed in saliva and nasal samples among participants with moderate to severe/critical SARS-CoV-2 infection. At the time of this primary analysis, the full viral load profile across the COVID-19 episode was only available for a limited number of COVID-19 cases. Information on the viral load over the course of the COVID-19 episode is available for 100 participants in the Ad26.COV2.S group and 274 participants in the placebo group with confirmed symptomatic COVID-19 with onset at least 14 days after vaccination.

Within the limitations described above, at this timepoint the data suggest that there is no significant difference in mean viral load from the onset of symptomatic COVID-19 episodes to resolution between the Ad26.COV2.S and placebo group. Results for cases with onset at least 28 days after vaccination are consistent with the results at least 14 days after vaccination.

7.1.6.8 Vaccine Efficacy Against US FDA Harmonized COVID-19 Definition

Because of the limited number of mild COVID-19 cases, the co-primary endpoints capture almost all observed symptomatic COVID-19 cases, hence the VE against any symptomatic disease and VE against COVID-19 per the US FDA harmonized definition (see Section 7.1.1.4 for definition details) are in line with the co-primary endpoints of VE against moderate to severe/critical disease. The VE (95% CI) against molecularly confirmed COVID-19 per the US FDA harmonized definition was in line with the observed VE against any symptomatic COVID-19: 67.2% (59.32;

73.67) and 66.7% (55.63; 75.23) at least 14 days and at least 28 days after vaccination, respectively (Table 1).

7.1.7 Efficacy in Subgroups

Vaccine efficacy against moderate to severe/critical COVID-19 and against severe/critical COVID-19 after a single dose of Ad26.COV2.S was in general observed across all subgroups evaluated (eg, region, age, sex, race, ethnicity, and serostatus) with varying degrees of protection. For subgroup analyses, a dataset was used including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation.

7.1.7.1 Efficacy by Region/Country

Across regions, VE against moderate to severe/critical COVID-19 (including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation) with onset at least 14 days and at least 28 days after vaccination ranged from 52.0% to 74.4% (Table 3). On a country level, the majority of the participants were enrolled in the US, Brazil, and South Africa. The number of cases reported in these countries allows for a robust country-specific evaluation of VE. The VE against severe/critical COVID-19 was consistently high across these countries when considering cases with an onset at least 14 days after vaccination.

7.1.7.2 Efficacy by Demographic and Baseline Characteristics: Age, Sex, Race, Ethnicity, Comorbidities and Location

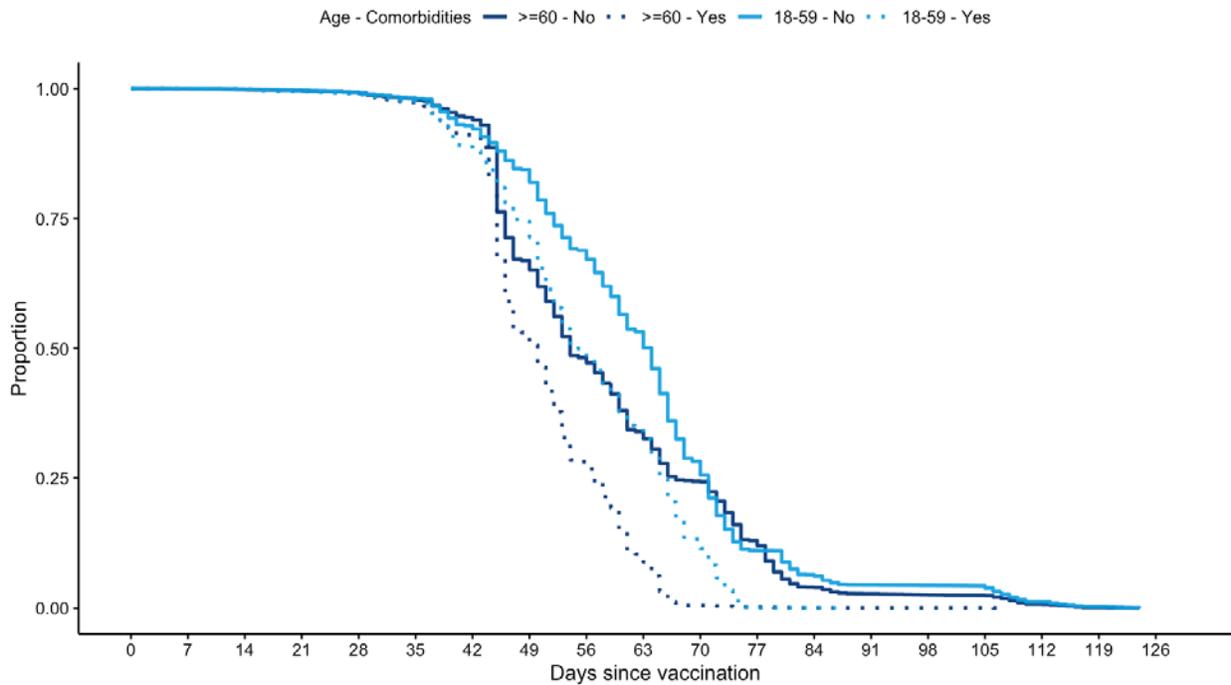
Vaccine efficacy against cases of moderate to severe/critical COVID-19 and against severe/critical COVID-19 after a single dose of Ad26.COV2.S was evaluated for subgroups where sufficient data are available, including age, comorbidities, sex, ethnicity, race, and regions (Figure 18 and Figure 19). The data represent cases confirmed and not confirmed by a central laboratory, except for the PP Risk Set (confirmed only). Additional data and longer follow-up observations will be gathered as the study continues to better understand findings for some subgroups (age and comorbidities, some of the countries, baseline SARS-CoV-2 serostatus, and HIV infection status).

For the subgroups with sufficient data for analysis, VE against moderate to severe/critical COVID-19 after a single dose of Ad26.COV2.S was in general observed across all subgroups with varying degrees of protection.

Participants ≥ 60 years of age without comorbidities had a higher VE estimate than participants ≥ 60 years of age with comorbidities. In addition to the difference in number of participants, another factor potentially driving the observed difference could be the length of follow-up after vaccination (see Figure 17). Per protocol design, vaccination of participants with comorbidities could start only after safety review of 2,000 participants without comorbidities. Therefore, the participants with comorbidities had a shorter follow-up time. The Kaplan Meier curves and plots of VE estimates over time suggest an increase in protection up to 50-60 days after immunization (see Figure 12). If, as presumed, this observation is related to the status of maturity of the immune responses, differences in follow-up time since exposure may be reflected in differences in VE between

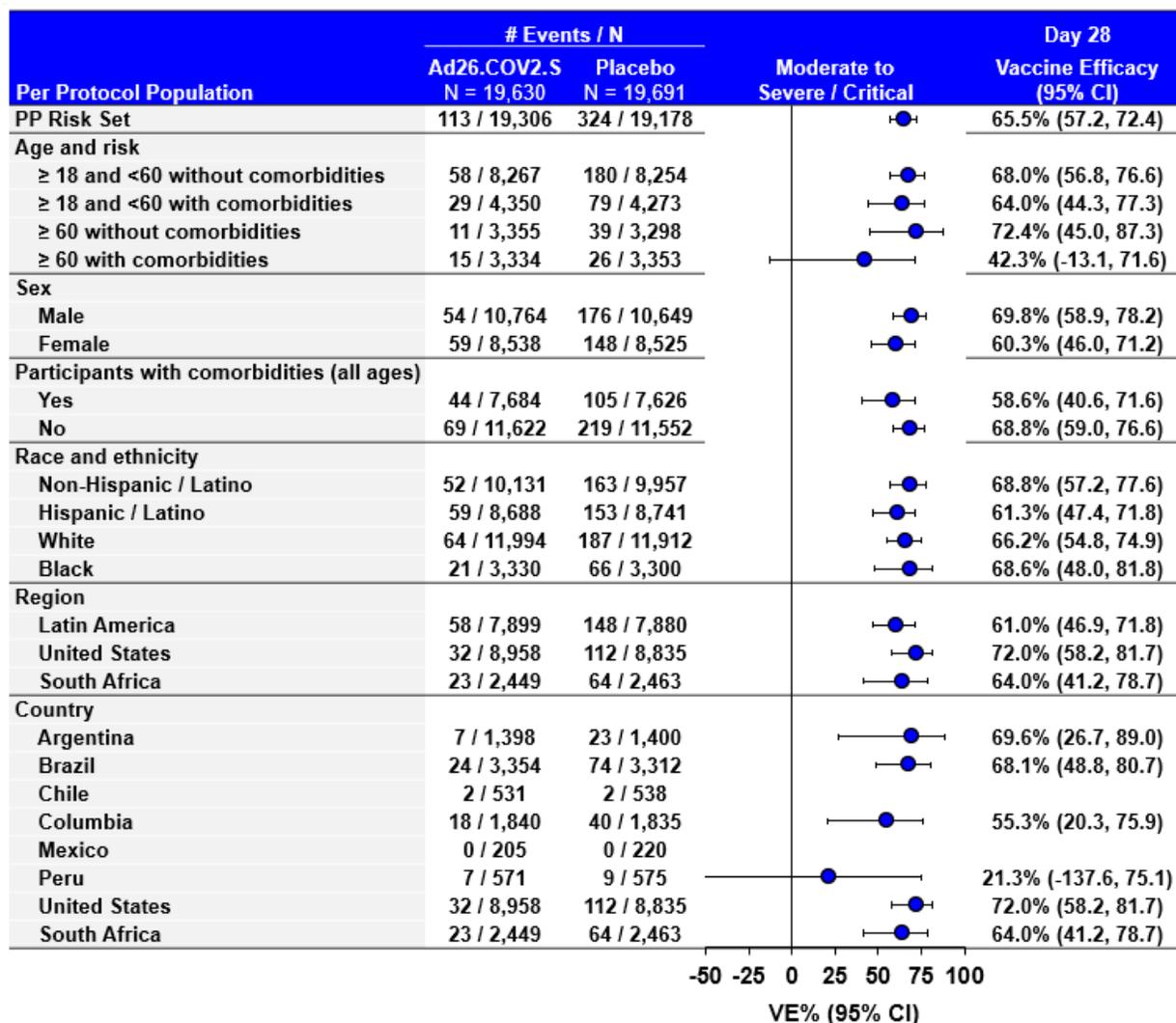
populations. More follow-up data will be gathered as the study continues to help understand currently observed potential differences between these subgroups.

Figure 17: Kaplan-Meier Curves of Time on Study by Age and Comorbidities; Per Protocol Analysis Set (VAC31518COV3001)



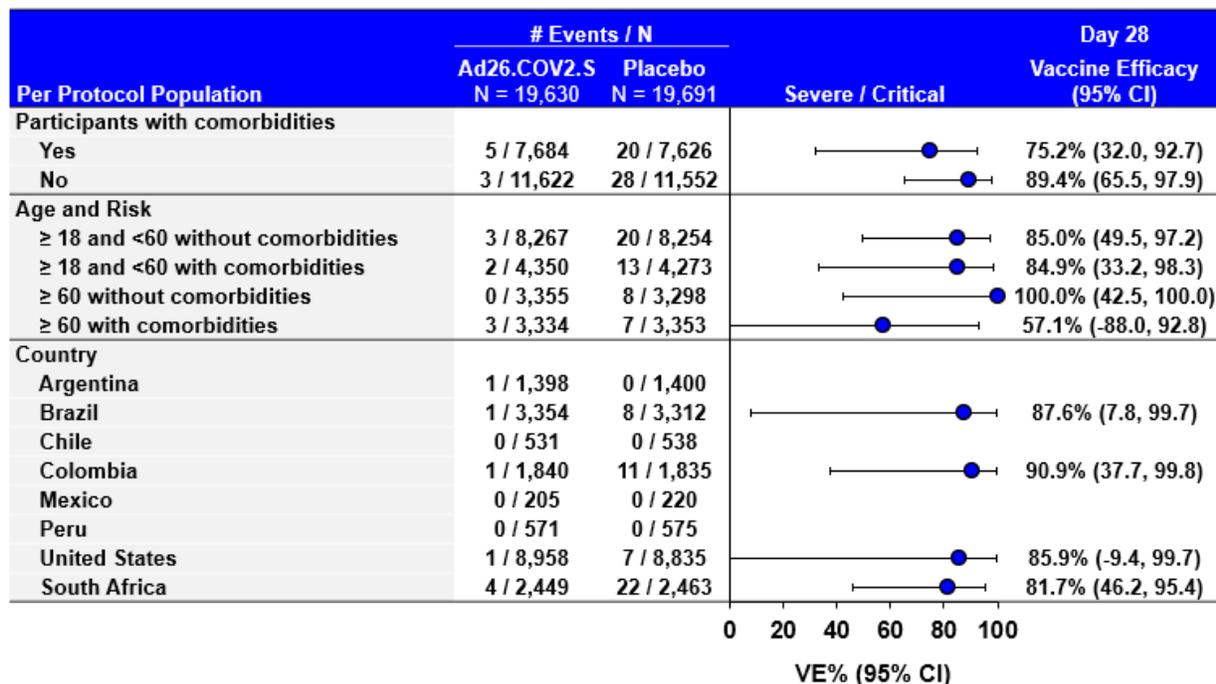
Solid dark blue line: ≥ 60 years of age without comorbidities
Dotted dark blue line: ≥ 60 years of age with comorbidities
Solid light blue line: ≥ 18 to < 60 years of age without comorbidities
Dotted light blue line: ≥ 18 to < 60 years of age with comorbidities

Figure 18: Vaccine Efficacy Against Moderate to Severe/Critical COVID-19 at Least 28 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001)



Note: Includes cases with a positive PCR from any source, regardless of central confirmation. The PP risk set excludes subjects who had a COVID-19 case with an onset before Day 29. Some subgroups have small numbers, reflected by the wide confidence intervals.

Figure 19: Vaccine Efficacy Against Severe/Critical COVID-19 at Least 28 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001)



Note: Includes cases with a positive PCR from any source, regardless of central confirmation
Some subgroups have small numbers, reflected by the wide confidence intervals.

7.1.7.3 *Efficacy in HIV-Infected Participants*

Based on the data available to date, no efficacy could be observed in HIV-infected participants (5 moderate to severe/critical cases with onset at least 14 days after vaccination in both the Ad26.COVS.2.S and placebo group and 2 vs 4 cases with onset at least 28 days after vaccination, respectively). However, the low number HIV-infected participants (<500 per vaccination group) resulted in a low number of person-years (approximately 70 per vaccination group) for case accrual, and available data do not suggest a negative impact of the vaccine. As the study continues, case accrual will continue and may allow for a better characterization of the VE in HIV-infected participants and a better understanding of potential differences between subgroups at the time of a subsequent analyses.

7.1.7.4 *Efficacy in Regions with Newly Emerging SARS-CoV-2 Strains*

In the US, where newly emerging strains were not predominant, VE (95% CI) against moderate to severe/critical COVID-19 was 74.4% (65.00; 81.57) and 72.0% (58.19; 81.71), when considering cases from at least 14 days and at least 28 days after vaccination, respectively. Vaccine efficacy (95% CI) against severe/critical COVID-19 in the US was 78.0% (33.13; 94.58) at least 14 days and 85.9% (-9.38; 99.69) at least 28 days after vaccination. Preliminary sequence data confirm that approximately 96% of these COVID-19 cases were due to the D614G variant and approximately 3% were due to the CAL.20C variant.

In South Africa, efficacy was observed against severe/critical COVID-19 and robust VE was observed for moderate to severe/critical COVID-19. This is especially important since preliminary sequence data confirm that approximately 96% (77/80 sequenced samples) of the COVID-19 cases that occurred in the study in South Africa were due to the SARS-CoV-2 variant 20H/501Y.V2 (belonging to the B.1.351 lineage), implying that Ad26.COV2.S is efficacious against this newly emerging and rapidly spreading strain. Vaccine efficacy (95% CI) against severe/critical COVID-19 was 73.1% (40.03; 89.36) at least 14 days after vaccination and increased to 81.7% (46.18; 95.42) at least 28 days after vaccination. An effect was also seen on mortality, since all COVID-19-associated deaths in the study, all in the placebo group, occurred in participants from South Africa. Vaccine efficacy (95% CI) against moderate to severe/critical COVID-19 was 52.0% (30.26; 67.44) at least 14 days and 64.0% (41.19; 78.66) at least 28 days after vaccination.

In Brazil, VE estimates were higher than those in South Africa and similar to those in the US. Preliminary sequence data confirm that approximately 71% (58/82 sequenced samples) of the COVID-19 cases in the study that occurred in Brazil appeared to be due to a variant from the P.2 lineage. This implies that efficacy in Brazil is not impacted by the high prevalence of the variant of the P.2 lineage as it is quite similar to the VE observed in the US, where D614G is highly prevalent (see Table 2).

For the immunogenicity results from participants in Brazilian, South African and US sites, refer to Section 6.5.

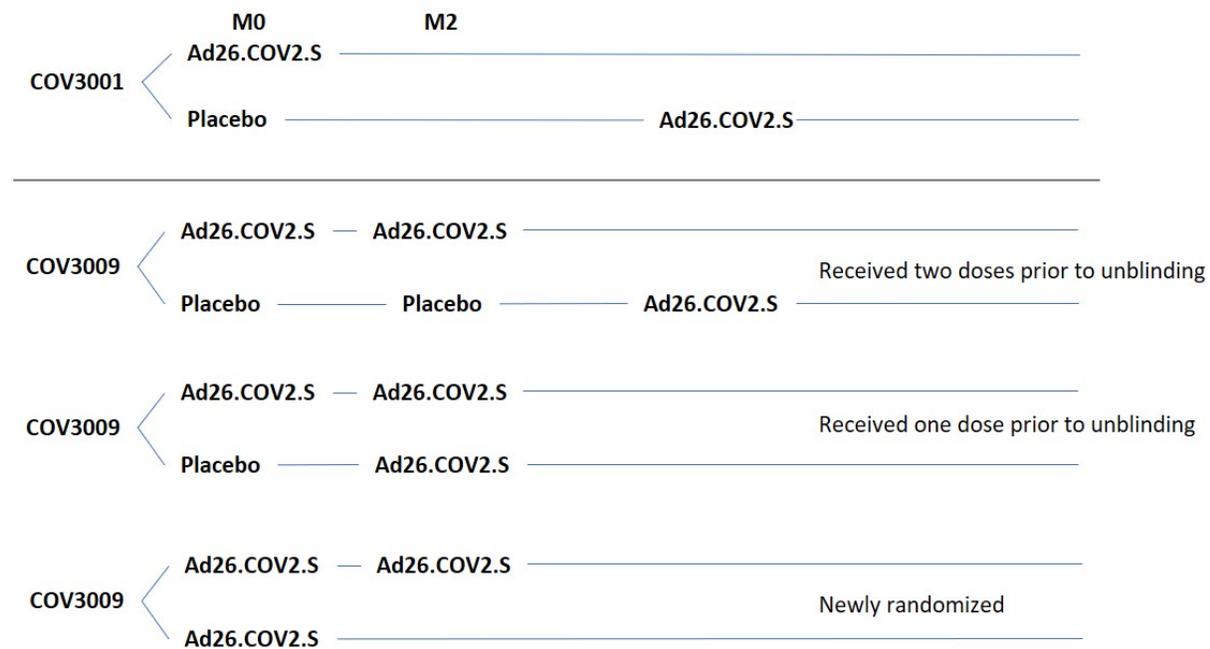
7.2 Proposed Amendment to Study Design for Placebo-controlled Studies with Ad26.COV2.S After Obtaining EUA

If the Ad26.COV2.S vaccine is granted an approval by at least one national regulatory authority (eg, EUA in the US), the COV3001 study design will be amended to facilitate cross-over of placebo participants in all participating countries to receive one dose of active study vaccine as fast as operationally feasible. Study investigators will be encouraged to consider current local public health guidance for determining the scheduling priority of participants. A protocol amendment describing the amended study design will be submitted to all regulatory authorities and ethics committees in the participating countries for review and approval. All participants will be encouraged to remain in the study and continue to be followed for efficacy/effectiveness, safety and immunogenicity as originally planned up to two years after vaccination. This will allow assessment of the duration of protection and immunogenicity of a single dose of Ad26.COV2.S by comparing two groups vaccinated approximately 4 to 6 months apart [60].

Janssen also proposes offering a single dose of Ad26.COV2.S to enrolled participants who initially received two doses of placebo in study COV3009. Because the study is expected to still be enrolling at the time of EUA, participants who received a first dose of placebo will receive a dose of Ad26.COV2.S as their second dose and participants yet to be enrolled will be randomized to either a single-dose or a two-dose schedule of Ad26.COV2.S. All participants will be encouraged to remain in the study and will be followed for efficacy, safety and immunogenicity as originally planned up to two years after vaccination. This will allow assessment of the level of efficacy and

duration of protection of a two-dose schedule of Ad26.COVS.2.S compared with the authorized single-dose schedule, as well as a direct comparison of the immunogenicity of the two schedules, whereby the single dose is introduced at different time points.

Figure 20: New Designs for Studies COV3001 and COV3009



For ongoing studies COV1001, COV1002, and COV2001, it is expected that crossover vaccination will be offered following similar principles as for COV3001 and COV3009, ie, open-label with vaccination of placebo participants will likely be the most feasible option. This needs to be evaluated in detail for each individual study and is to be discussed with authorities in the countries where the studies are taking place. For any future study in the program, the use of placebo control will become challenging, at least for populations in which EUA or similar authorization will be obtained.

8 CLINICAL SAFETY AND REACTOGENICITY

Summary

- Overall, safety data from the Phase 3 study COV3001 from 43,783 participants with a median of 2 months of follow-up after vaccination demonstrate that a single dose of Ad26.COV2.S has an acceptable safety and reactogenicity profile in participants ≥ 18 years of age, including adults ≥ 60 years of age.
- Lower reactogenicity was observed for older adults (≥ 60 years of age) compared to younger adults (≤ 18 to < 60 years of age) among participants vaccinated with Ad26.COV2.S.
- The safety profile of Ad26.COV2.S is further supported by data from more than 193,000 individuals who have been exposed to Janssen's AdVac[®]-based vaccines in the context of other clinical studies and programs.
- Most AEs were of mild or moderate severity, were transient in nature and generally resolved within 1 to 2 days post vaccination.
- Overall, there were 19 deaths in the study: 3 in the vaccine group versus 16 in the placebo group. None of the deaths were deemed related to vaccination. There were no deaths confirmed to be associated with COVID-19 in the Ad26.COV2.S group. Six of the deaths in the placebo group were "confirmed COVID-19-associated" and 2 were classified as "probable COVID-19 associated". One of the confirmed deaths had a positive PCR test result at baseline.
- There was no clinical evidence of VAED, including VAERD, supporting the nonclinical observations that the theoretical risk of VAED is low.

8.1 Introduction and Methodology

The most extensive safety information of the selected vaccine regimen (ie, a single dose of Ad26.COV2.S at 5×10^{10} vp) is available from the pivotal Phase 3 study COV3001 on $\geq 44,000$ participants ≥ 18 years of age, and that study is the focus of this safety discussion. The safety analysis of study COV3001 was performed once the required 2-month median follow-up (defined as a minimum of 8 weeks of median follow-up post vaccination) was reached (on 22 January 2021). The study was under the supervision of an independent data safety monitoring board (DSMB). For study COV3001, summaries of solicited and unsolicited AEs are based on the Safety Subset (ie, a subset of the FAS) and summaries of deaths, SAEs, MAAEs, and AEs leading to study discontinuation are based on the FAS. The safety data presented in Section 8.4 focus on the pivotal Phase 3 study COV3001 and supporting clinical safety experience from other studies is summarized in Section 8.6. In addition, safety data from Janssen conducted clinical studies with Ad26-based vaccines is considered to be supportive of the Ad26.COV2.S safety profile and is discussed in Section 8.5.

Unless otherwise specified, AEs for study COV3001 were collected as follows:

- Solicited local and systemic AEs (reactogenicity), from the day of vaccination until 7 days after vaccination:
 - Solicited local AEs: injection site pain/tenderness, erythema, and swelling.
 - Solicited systemic AEs: fatigue, headache, nausea, myalgia, and pyrexia/fever (body temperature $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$).
- Unsolicited AEs, from the day of vaccination until 28 days after vaccination.
- Serious AEs (SAEs), including deaths, and any AEs leading to study discontinuation from the day of first vaccination until the end of the study.
- MAAEs from the day of vaccination until 6 months after vaccination, except for MAAEs leading to study discontinuation which are being reported during the entire study.

Solicited local AEs were considered as related to the study vaccine by definition and, regardless of investigator assessment, are described as appropriate in the proposed product labelling. Solicited systemic and unsolicited AEs were considered related to the use of the study vaccine as per investigator assessment.

Allergic reactions of interest as severe reactions (eg, hypersensitivity reactions and anaphylaxis) are known to occur with any injectable vaccine. In addition, based on clinical data as well as data from ongoing studies and publications, and based on regulatory interactions, additional AEs of interest that represent various diseases and conditions including, but not limited to immune-mediated and (neuro-)inflammatory events (eg, Guillain-Barré Syndrome, Bell's palsy) and thrombotic and thromboembolic events (eg, PE, DVT) were selected for further evaluation.

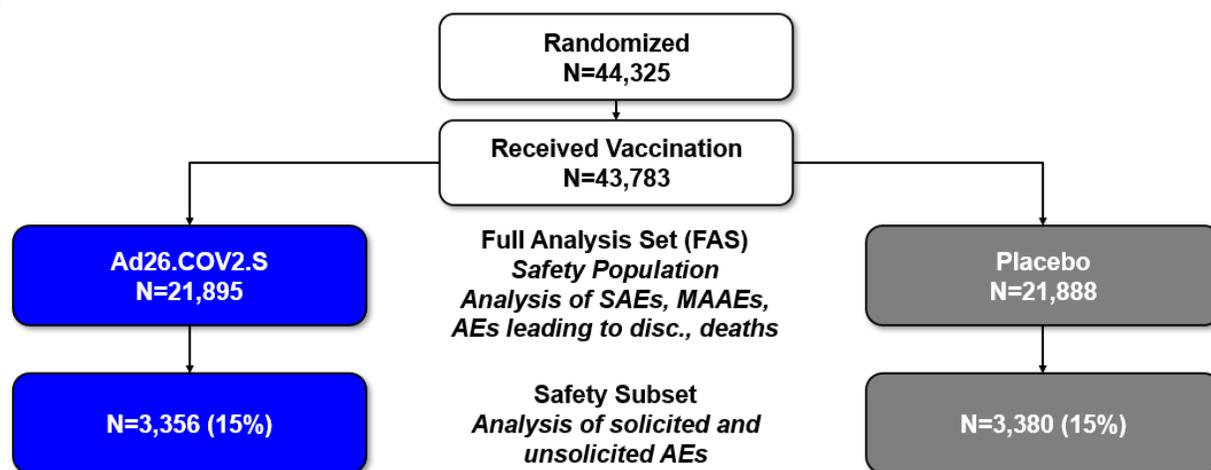
No clinical laboratory evaluations were conducted in study COV3001. Vital signs that were considered clinically significant in the opinion of the investigator were to be reported as AEs.

8.2 Safety Population

Data for AEs reported in the safety subset of 6,736 participants (3,356 in the Ad26.COV2.S group and 3,380 in the placebo group) include solicited AEs collected from the day of vaccination until 7 days afterwards, and unsolicited AEs collected from the day of vaccination until 28 days afterwards.

Data on deaths, SAEs, MAAEs, and AEs leading to discontinuation and events of interest were collected on all 43,783 participants in the FAS who received a study vaccination (21,895 in the Ad26.COV2.S group and 21,888 in the placebo group); these participants were followed for a median time of 58 days after vaccination. Importantly, a substantial portion of this population were at high risk for contracting COVID-19. Nearly 20% of the FAS were frontline essential workers or health care professionals.

Figure 21: Disposition of the Safety Population and Subset (Study COV3001)



Overall, the demographic profile was generally similar in the safety subset and the FAS, with the exception of race, country, and serostatus at baseline. The proportion of White participants was greater in the safety subset (83.4%) compared to the FAS (58.7%). The proportion of participants from Brazil was greater in the safety subset (38.5%) compared to the FAS (16.6%). The proportion of participants who were SARS-CoV-2 seropositive at baseline was lower in the safety subset (4.5%) compared to the FAS (9.6%).

In addition, the demographic profile of participants with comorbidities was also generally similar, with the exception of a higher median BMI in participants with at least one comorbidity. Despite minor differences in the demographic profile between the FAS and the safety subset, the safety subset allows for a robust description of solicited and unsolicited events of the vaccine (representative of the FAS).

8.3 Vaccine Exposure

Among the 43,783 participants in the FAS who received a study vaccination, the median follow-up after vaccination was 58 days, and 23,903 (54.6%) participants had at least 2 months (8 weeks) of follow-up at the time of the primary analysis. Longer safety follow-up of >2 months is available for over 23,000 participants in the FAS (11,948 participants in the Ad26.COVID.2.S group and 11,955 in the placebo group).

In the safety subset of 6,736 vaccinated participants (3,356 in the Ad26.COVID.2.S group and 3,380 in the placebo group), 99.9% of the participants in each vaccine group completed the post-vaccination follow-up period of Day 1-29.

In total, 8 pregnancies were reported in the Global Medical Safety database for the COV3001 study. Five pregnancies are ongoing, one pregnancy resulted in an elective abortion, one in a spontaneous abortion and one pregnancy was reported as unknown/not reported.

8.4 Adverse Events

8.4.1 *Solicited Adverse Events*

Ad26.COV2.S has an acceptable reactogenicity profile in participants ≥ 18 years of age. Reactogenicity was demonstrated to be transient and most solicited AEs generally resolved in 1 to 2 days post vaccination. Most solicited AEs were Grade 1 or Grade 2 in severity. The frequency of Grade 3 solicited AEs was low overall, but higher after vaccination with Ad26.COV2.S compared to placebo. No Grade 4 solicited local AEs were reported.

No clinically relevant differences in the reactogenicity profile of Ad26.COV2.S were observed across sex, race/ethnicities, geographies, comorbidities, SARS-CoV-2 or HIV serostatus at baseline.

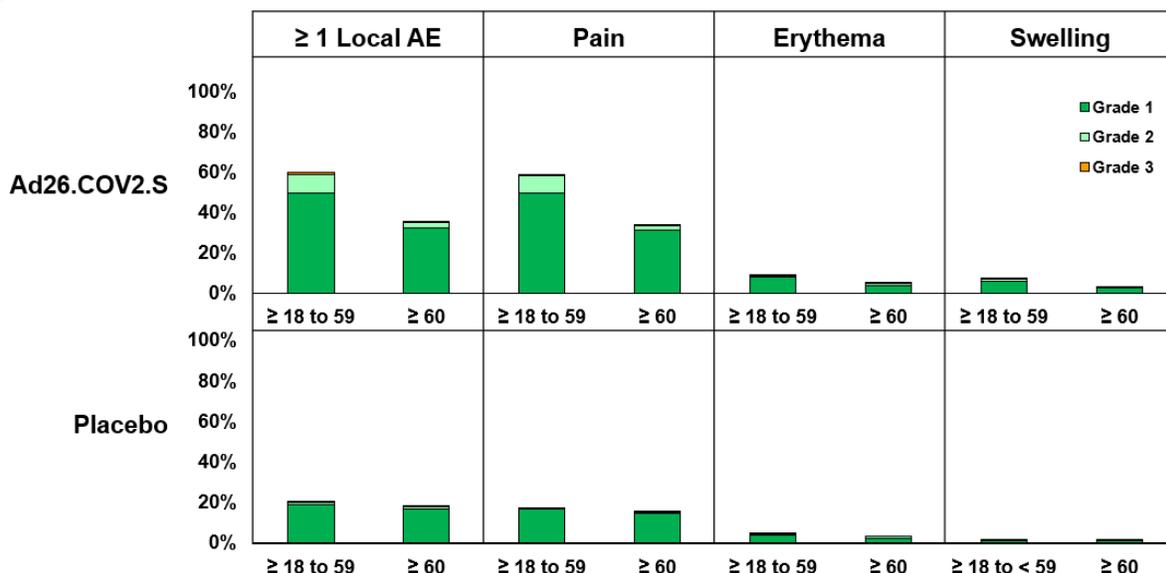
The frequency of solicited AEs was lower in participants aged ≥ 60 years compared to participants aged ≥ 18 to < 60 years. Participants with one or more comorbidity (ie, asthma, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease [COPD], serious heart conditions, hypertension, and obesity) at baseline had higher frequencies of solicited AEs in the Ad26.COV2.S group compared to placebo .

8.4.1.1 *Solicited Injection Site (Local) Adverse Events*

Most solicited local AEs were Grade 1 or Grade 2 in severity. All Grade 3 solicited local AEs were reported in $\leq 1.0\%$ of participants in the Ad26.COV2.S group. No Grade 4 solicited local AEs were reported. All solicited local AEs were transient in nature.

Figure 22 shows the most frequently reported solicited vaccination site reactions. Vaccination site pain was reported by 1,634 (48.7%) participants in the Ad26.COV2.S group, vaccination site erythema and swelling were reported in $< 8\%$ of participants in the Ad26.COV2.S group. The most frequently reported Grade 3 AE was vaccination site pain reported in 11 (0.3%) participants in the Ad26.COV2.S group. Vaccination site erythema and vaccination site pain had a median duration of 2 days after vaccination with Ad26.COV2.S and vaccination site swelling had a median duration of 3 days after vaccination with Ad26.COV2.S.

Figure 22: Most Frequently Reported Solicited Injection Site (Local) Adverse Events in Study COV3001 (Safety Subset)



8.4.1.2 *Solicited Systemic Adverse Events*

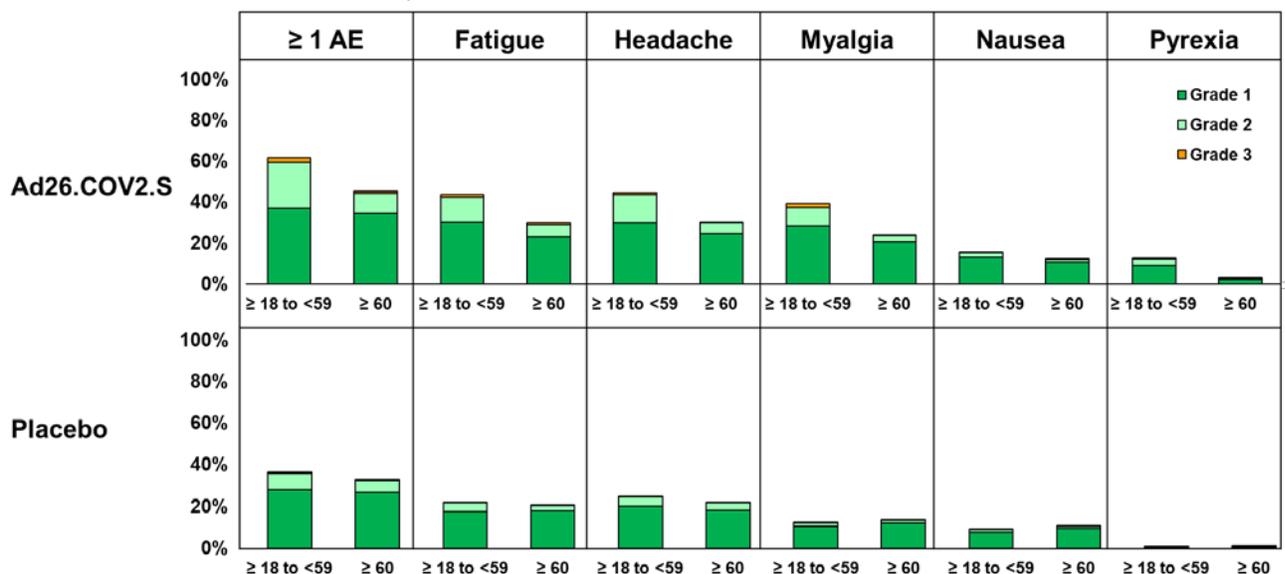
Most solicited systemic AEs were Grade 1 or Grade 2 in severity. All Grade 3 solicited systemic AEs were reported in <2.0% of participants in the Ad26.COVS.S group. No Grade 4 solicited systemic AEs were reported. Most solicited systemic AEs were considered related to the study vaccine by the investigator. Most solicited systemic AEs were transient in nature and had a median duration of 1 to 2 days after vaccination with Ad26.COVS.S.

Figure 23 shows the most frequently reported solicited systemic site reactions. The most frequently reported solicited systemic AEs in the Ad26.COVS.S group were fatigue (38.2%), headache (39.0%), and myalgia (33.2%). Other solicited systemic AEs were reported in <15% of participants in the Ad26.COVS.S group.

Pyrexia (fever defined as body temperature $\geq 38.0^{\circ}\text{C}$, as recorded by the participants) of any grade was reported in 302 (9.0%) of participants in the Ad26.COVS.S group. Grade 3 pyrexia was reported in 8 (0.2%) of participants in the Ad26.COVS.S group of which the majority occurred in the younger age group (below 35 years of age). All solicited cases of fever were reported to have started on the day of vaccination (Day 1) or the day after (Day 2) and had a median duration of 1 day.

Analgesics and antipyretics were recommended post-vaccination for symptom relief as needed. Acetaminophen, metamizole sodium, and ibuprofen were the most frequently used medications. Of the 302 participants who experienced fever in the Ad26.COVS.S group, 202 (66.9%) used antipyretics. Overall, in the FAS, 1,128/21,895 (5.2%) participants in the Ad26.COVS.S group used analgesics or antipyretics up to 7 days post vaccination.

Figure 23: Most Frequently Reported Solicited Systemic Adverse Events in Study COV3001 (Safety Subset)



8.4.2 Unsolicited Adverse Events

Overall, there was no apparent difference in unsolicited AEs reported in the Ad26.COV2.S group compared to the placebo group. Most unsolicited AEs were Grade 1 or Grade 2 in severity. Unsolicited AEs of \geq Grade 3 in severity and considered related to the study were infrequent in the Ad26.COV2.S group (0.1% or less).

All unsolicited AEs (by SOC and PT) reported during the 28-day post-vaccination phase had a frequency below 10%. The most frequently reported related unsolicited AEs in the Ad26.COV2.S group were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs not recorded as solicited AEs, were chills, arthralgia, cough, nasal congestion, and diarrhea. Most were of mild or moderate severity and most were considered not related to the study vaccine by the investigator. Other unsolicited AEs were reported in $<1.0\%$ of participants in the Ad26.COV2.S group.

The frequency of unsolicited AEs that were considered related to study vaccine by the investigator was higher in participants in the Ad26.COV2.S group (242/440 [55%]) compared to participants in the placebo group (154/407 [37.8%]).

During the 28-day period post-vaccination, there were 19 (0.6%) participants experienced unsolicited AEs of at least Grade 3 in the Ad26.COV2.S group. Of these, 5 (0.1%) were considered to be related to the study vaccine in the Ad26.COV2.S group (Table 15).

Table 15: Number of Participants with Unsolicited Adverse Events of at Least Grade 3 and Related to Vaccination by System Organ Class and Preferred Term in COV3001 (Safety Subset)

	Ad26.COVID.S N=3,356	Placebo N=3,380
Participants with one or more AEs ≥ Grade 3 considered related to study vaccine	5 (0.1%)	1 (<0.1%)
General disorders and administration site conditions	3 (0.1%)	0
Chills	1 (<0.1%)	0
Fatigue	1 (<0.1%)	0
Malaise	1 (<0.1%)	0
Gastrointestinal disorders	1 (<0.1%)	0
Diarrhea	1 (<0.1%)	0
Musculoskeletal and connective tissue disorders	1 (<0.1%)	1 (<0.1%)
Pain in extremity	1 (<0.1%)	0
Arthralgia	0	1 (<0.1%)
Nervous system disorders	1 (<0.1%)	1 (<0.1%)
Headache	1 (<0.1%)	0
Dizziness	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1%)
Nasal congestion	0	1 (<0.1%)
Sneezing	0	1 (<0.1%)
Wheezing	0	1 (<0.1%)

8.4.3 MAAEs, Deaths, SAEs

Overall, MAAEs, SAEs and deaths were recorded at a higher proportion in the placebo group. MAAEs were infrequent and occurred at similar rates in the Ad26.COVID.S and placebo groups. A numerical imbalance was observed in the overall number of fatal and non-fatal SAEs between the Ad26.COVID.S group (90) and placebo group (137). Additional analysis of non-COVID-19 associated SAEs showed a balanced distribution of SAEs between both vaccine groups with 83 (0.4%) participants reporting at least one non-COVID-19 associated SAE in the Ad26.COVID.S group compared to 96 (0.4%) participants in the placebo group (Table 18).

8.4.3.1 *Medically-attended Adverse Events*

A total of 304 (1.4%) participants reported one or more MAAEs in the Ad26.COVID.S group compared to 408 (1.9%) participants in the placebo group. The most frequently reported MAAEs (≥0.5% of participants in any vaccine group) were infections and infestations by SOC. No single MAAE occurred in >1.0% of participants or by SOC in either group.

The greater frequency of MAAEs in the placebo group in part reflected the greater number of COVID-19 cases. Indeed, COVID-19 infection was the most frequently reported MAAE for 16 (0.1%) participants in the Ad26.COVID.S group compared to 35 (0.2%) participants in the placebo group. Other COVID-19 associated AEs included COVID-19 pneumonia (5 versus 9 participants) and pneumonia (4 versus 7 participants).

Other MAAEs for which a numerical imbalance was observed between the Ad26.COV2.S group and the placebo group include but are not limited to urinary tract infection (9 versus 17 participants) and upper respiratory tract infection (4 versus 10 participants). Furthermore, a higher number of participants reported arthralgia as an MAAE in the Ad26.COV2.S group (7 participants) compared to the placebo group (2 participants).

None of the MAAEs led to study discontinuation.

8.4.3.2 *Deaths*

Up to the cut-off date of 22 January 2021, 19 deaths were reported in study COV3001: 3 in the Ad26.COV2.S group (lung abscess, non-COVID-19 pneumonia, and one of unknown cause [onset on Day 45]) and 16 in the placebo group, all of which were considered unrelated to the study vaccine (Ad26.COV2.S or placebo) by the investigator (Table 16).

Six of the 16 deaths in the placebo group were confirmed (by positive RT-PCR test) to be associated with COVID-19. It should be noted however, that one of the deaths in the placebo group was reported as COVID-19 pneumonia with an onset 10 days post vaccination and who had a positive SARS-CoV-2 RT-PCR test at baseline. None of the 3 deaths in the Ad26.COV2.S group were associated with COVID-19 (Table 15).

For those deaths for which no SARS-CoV-2 RT-PCR test result was available, the likelihood of fatal SAEs being associated with COVID-19 was assessed based on the available information (narratives by the investigator, laboratory data, and reported clinical symptoms) against the WHO COVID-19 case definition (suspected, probable, confirmed COVID-19 events [not deaths]) [1]. Cases not meeting the criteria for COVID-19 were classified as “Not COVID-19.”

Out of the 16 deaths reported in the placebo group, 6 cases were classified as “Confirmed COVID-19” based on WHO case definition and a further two were classified as “Probable COVID-19”. There were no cases classified as suspected according to the WHO criteria.

The remainder of the deaths in the Ad26.COV2.S group and placebo group were assessed as “Not-COVID-19” based on the WHO case definition. The imbalance in terms of COVID-19 associated deaths is consistent with the clinical database findings in terms of severity of COVID-19 in the Ad26.COV2.S group versus the placebo group.

Table 16: Listing of Fatal Adverse Events in Study COV3001 (FAS)

Vaccination Group	Cause of death as reported by the investigator	Positive SARS-CoV-2 RT-PCR during the study	Day of AE Onset ^a	Duration (days)	COVID-19 Cases as per Janssen WHO clinical assessment ^b
Ad26.COVS.S	Death		45	1	Not COVID-19
	Lung abscess ^c		33	27	Not COVID-19
	Pneumonia ^c		11	14	Not COVID-19
Placebo	Completed suicide		25	1	Not COVID-19
	Acute myocardial infarction		62	1	Not COVID-19
	Death		25	1	Not COVID-19
	Death		41	1	Not COVID-19
	Pneumonia		59	3	Not COVID-19
	Accidental overdose		7	1	Not COVID-19
	Sudden death		58	1	Not COVID-19
	COVID-19	Yes	25	14	Confirmed COVID-19
	Cardiac failure	Yes	15	1	Confirmed COVID-19
	Pneumonia		27	2	Probable COVID-19
	Malaise ^e		.	.	Not COVID-19
	COVID-19	Yes	32	8	Confirmed COVID-19
	Suspected COVID-19		23	4	Probable COVID-19
	COVID-19 pneumonia ^d	Yes	10	9	Confirmed COVID-19
	COVID-19	Yes	28	4	Confirmed COVID-19
COVID-19 pneumonia	Yes	46	10	Confirmed COVID-19	

Key: AE=adverse event

^aDay of AE Onset is in reference to the date of first vaccination.

^b WHO COVID-19: Case Definitions, published 16 December 2020.

^c Had a negative COVID-19 test result indicated in Council for International Organizations of Medical Sciences (CIOMS) form.

^d Had a positive PCR result at baseline.

^e Possibly diabetes related, no formal cause of death reported

Note: AEs are coded using MedDRA Version 23.0.

8.4.3.3 *Serious Adverse Events*

A total of 227 participants (90 [0.4%] in the Ad26.COVS.S group and 137 [0.6%] in the placebo group) reported one or more SAEs in the FAS. Of these 227 participants, 9 (<0.1%) participants reported a total of 10 SAEs (7 in the Ad26.COVS.S group and three in two participants in the placebo group) which were considered by the investigator to be related to the study vaccine (Table 17).

For the following related SAEs, refer to the Sections as indicated below for further details.

- Grade 4 Guillain-Barré syndrome (Ad26.COVS.S group), Section 8.4.6.5
- Grade 4 DVT (placebo group), Section 8.4.6.4
- Grade 3 Type IV hypersensitivity (Ad26.COVS.S group), Section 8.4.6.1
- Grade 2 facial paralysis (Bell's Palsy) (both in the Ad26.COVS.S group), Section 8.4.6.6

Other related SAEs reported in the Ad26.COVS.S group:

- Grade 4 pericarditis was reported in a participant approximately 17 days following vaccination and resulted in hospitalization. The event resolved within 5 days after treatment and the participant was discharged. The event was assessed as indeterminate as per WHO AEFI criteria, however due to close temporal association and a lack of other explanatory factors it was assessed as possibly related by Janssen for reporting purposes.
- Grade 3 brachial radiculitis was reported in a participant with immediate onset following vaccination. The participants symptoms worsened and by Day 3 the participant visited the emergency department with dysesthesia. Examinations revealed signs of paresthesia, anxiety disorder, acute pain, and allodynia of non-established origin. Treatment included naproxen and hydrocodone/acetaminophen; however, there was no improvement in the pain. The SAE was ongoing for 75 days at the time of reporting and was reported as not resolved. Based on the clinical symptoms, and electroconductive studies, Janssen concluded that the case did not meet the clinical definition of brachial neuritis, with injection site pain secondary to injection being the most likely alternative diagnosis.
- Grade 3 post-vaccination syndrome was reported in a participant 2 days following vaccination and the participant was hospitalized due to exacerbated generalized weakness originally suspected for demyelinating disorder which was subsequently discarded. The event resolved within 3 days and the participant was discharged. Based on the symptoms, the event was assessed as vaccine reactogenicity (asthenia) by Janssen.

Other related SAEs, reported in the placebo group:

- Grade 3 Epstein-Barr virus (EBV) infection and a Grade 3 atrial flutter were reported in the same participant 14 and 21 days following vaccination, respectively. At the time of reporting, the participant was recovering from the EBV infection and the atrial flutter had resolved. Both SAEs were considered related to the study vaccine by the investigator and not related by Janssen. EBV infection was not considered related to the study vaccine by Janssen due to biological implausibility, and atrial flutter was assessed as likely secondary to EBV.

One SAE of transverse sinus thrombosis resulting in cerebral hemorrhage was initially considered to be related to blinded study vaccine and led to a pause in study vaccination in all ongoing Ad26.COV2.S clinical studies. After review of available information and follow-up assessments by the investigator, the causality was reassessed as not related to the study vaccine by the investigator and Janssen based on the participant's pre-existing medical conditions. After unblinding, it was determined that the participant was in the Ad26.COV2.S group.

Table 17: Serious Adverse Events Related to Vaccination

Vaccination Group	Age/ Sex	Comorbidities at Baseline	Preferred Term	Day of AE Onset ^a	Duration (days)	Severity Grade/ Relationship to Vaccine ^b
Ad26.COV2.S	68/M	Yes	Pericarditis	17	5	Grade4/Related
	62/M	Yes	Facial paralysis	3	43*	Grade2/Related
	30/M	No	Radiculitis brachial	1	75*	Grade3/Related
	60/F	No	Guillain-Barre syndrome	16	29*	Grade4/Related
	35/M	Yes	Post vaccination syndrome	2	3	Grade3/Related
	43/M	Yes	Facial paralysis	16	24*	Grade2/Related
	42/M	No	Vaccination site hypersensitivity	3	31	Grade3/Related
Placebo	44/M	No	Deep vein thrombosis	6	42*	Grade4/Related
	69/M	Yes	Epstein-Barr virus infection ^c	14	28	Grade3/Related
			Atrial flutter ^c	21	3	Grade3/Related

Key: AE=adverse event

* Ongoing at time of reporting.

^a Day of AE Onset is in reference to the date of first vaccination.

^b Relationship to vaccine is assessed by the investigator.

^c Reported in the same participant

Note: AEs are coded using MedDRA Version 23.0.

As a numerical imbalance was observed in the overall number of non-fatal SAEs between the Ad26.COV2.S group (90) and placebo group (137), an additional analysis of non-COVID-19 SAEs was performed. Any SAEs associated with either COVID-19 or SARS-COV-2 were excluded from this analysis. A total of 83 (0.4%) participants reported at least one non-COVID-19 SAE in the Ad26.COV2.S group compared to 96 (0.4%) participants in the placebo group, showing no imbalance of non-COVID-19 related SAEs between groups by SOC (Table 18). There were no notable patterns or numerical imbalances suggesting a causal relationship to the vaccine or safety signals identified.

Table 18: Serious Adverse Events not associated with COVID-19 by System Organ Class in Study COV3001 (FAS)

System organ class	Ad26.COV2.S N=21,895	Placebo N=21,888
Participants with 1 or more SAEs	83 (0.4%)	96 (0.4%)
Infections and infestations	23 (0.1%)	27 (0.1%)
Nervous system disorders	10 (<0.1%)	8 (<0.1%)
Respiratory, thoracic and mediastinal disorders	10 (<0.1%)	4 (<0.1%)
Injury, poisoning and procedural complications	9 (<0.1%)	9 (<0.1%)
General disorders and administration site conditions	5 (<0.1%)	7 (<0.1%)
Gastrointestinal disorders	4 (<0.1%)	8 (<0.1%)
Hepatobiliary disorders	4 (<0.1%)	1 (<0.1%)
Cardiac disorders	3 (<0.1%)	14 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (<0.1%)	4 (<0.1%)
Renal and urinary disorders	3 (<0.1%)	5 (<0.1%)
Vascular disorders	3 (<0.1%)	4 (<0.1%)
Metabolism and nutrition disorders	2 (<0.1%)	5 (<0.1%)
Pregnancy, puerperium and perinatal conditions	2 (<0.1%)	1 (<0.1%)
Psychiatric disorders	2 (<0.1%)	6 (<0.1%)
Eye disorders	1 (<0.1%)	0
Musculoskeletal and connective tissue disorders	1 (<0.1%)	1 (<0.1%)
Skin and subcutaneous tissue disorders	1 (<0.1%)	1 (<0.1%)
Surgical and medical procedures	1 (<0.1%)	0
Reproductive system and breast disorders	0	2 (<0.1%)

Key: SAE=serious adverse event

Note: Participants are counted only once within a phase for any given event, regardless of the number of times they actually experienced the event in that phase.

8.4.4 Vaccine-Associated Enhanced Disease

Based on past experiences in the development of vaccines against RSV, Dengue virus, SARS-CoV, and MERS-CoV, there is a theoretical risk for VAED, including VAERD, for SARS-CoV-2 vaccines. As COVID-19 clinical manifestations are not limited to respiratory symptoms, not only VAERD, but also the broader term VAED is being considered.

Clinical data following a single dose of Ad26.COV2.S did not indicate any evidence of VAED, including VAERD, which confirms the nonclinical observations that the theoretical risk of VAED is low. The observed VAERD in nonclinical studies with SARS-CoV and MERS-CoV based vaccines were attributed to induction of a Th2-skewed immune response. The interim analysis of the clinical study COV1001 clearly indicates that Ad26.COV2.S is able to elicit a cellular response with Th1-skewed CD4+ response as well as to induce a high level of neutralizing antibodies, both of which are considered desirable to prevent predisposition to VAERD. In addition, VE of Ad26.COV2.S against confirmed severe/critical COVID-19 was established, with >5 severe/critical COVID-19 cases in the placebo group and a favorable split of 5 cases in the Ad26.COV2.S group with an onset at least 28 days after vaccination and 34 cases in the placebo group. The overall number of SAEs was higher in the placebo group vs the Ad26.COV2.S group mainly due to COVID-19 associated events, as well as the number of COVID-19 associated deaths was also higher in the placebo group (Table 5). In addition, for both moderate and severe/critical

COVID-19 cases reported in the efficacy evaluations, symptoms in the Ad26.COVS group were on average milder than in the placebo group. Janssen has shown absence of enhanced lung pathology, absence of increased viral load and absence of enhanced clinical signs of disease in Ad26.COVS-immunized and SARS-CoV-2 challenged Syrian hamsters and NHP as compared to challenged controls, even under conditions of suboptimal immunity allowing breakthrough infection [51, 52]. The sum of available nonclinical and clinical data suggest that the theoretical risk of VAED, including VAERD, for Ad26.COVS is low.

8.4.5 Immediate Adverse Events

The first 2,000 participants in each of the two age groups (≥ 18 to < 60 years and ≥ 60 years) remained under observation at the study site for at least 30 minutes after vaccination to monitor for immediate reactions. No early onset had been observed in either age group at the time of the Day 3 safety review of the initial 2,000 participants; therefore, the observation period at the study site was reduced to at least 15 minutes for the remaining participants in the study.

Immediate hypersensitivity reactions following vaccination were rare and nonserious. No 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.COVS and placebo groups. Solicited and unsolicited immediate AEs occurring within 30 minutes after vaccination were infrequent. Frequencies of solicited and unsolicited immediate AEs were similar in participants in the Ad26.COVS group (0.5%) compared to participants in the placebo group (0.3%). None of the immediate events reported in the Ad26.COVS and placebo groups were considered serious. These findings are consistent with the overall safety data of the Ad26 vector platform.

8.4.6 Adverse Events of Interest

Based on data from ongoing studies and publications, as well as on regulatory interactions, AEs of interest that represent various diseases and conditions including, but not limited to allergic reactions, immune mediated and (neuro) inflammatory events (eg, Guillain-Barré Syndrome, Bell's palsy), and thrombotic and thromboembolic events (eg, PE, DVT) were selected for further evaluation. Besides the numerical imbalances described in the subsections below, there were no notable patterns or numerical imbalances between the Ad26.COVS and placebo group in the FAS for specific categories of (S)AEs (including neurologic, neuroinflammatory, and cardiovascular events) that would suggest a causal relationship to the Ad26.COVS vaccine. The absence of a causal link is further enforced by the safety data from the platform. In addition, the overall total number of cases of AEs of interest observed in the study were low and within the rates observed in the general population.

8.4.6.1 Allergic Reactions (Hypersensitivity) and Severe Allergic Reactions (Anaphylaxis)

In general, hypersensitivity reactions are a rare occurrence within the Ad26 platform. Severe allergic reactions (anaphylaxis) have not been reported in Ad26.COVS clinical studies and have not been identified as a safety issue in the broader safety dataset for Ad26-based vaccines.

In COV3001, the most frequently reported AEs within the broad Standardised MedDRA Queries (SMQ) ‘non-anaphylactic allergic reactions’ (≥ 6 participants in the Ad26.COV2.S group) were rash (24 Ad26.COV2.S, 16 placebo), urticaria (8 Ad26.COV2.S, 3 placebo), and hypersensitivity (6 Ad26.COV2.S, 4 placebo). Events of urticaria and rash were considered as likely related to the vaccine. Further assessment of the events under the PT ‘hypersensitivity’ showed most of these events to be either seasonal allergies or allergy to a medication other than the vaccine.

The AEs within the broad SMQ ‘anaphylactic reaction’ were infrequent ($\leq 0.1\%$) in both the Ad26.COV2.S group and placebo group. A total of 15 participants in the Ad26.COV2.S group and 8 participants in the placebo group developed an AE within the aforementioned SMQ. However, upon further evaluation, all reported events correspond to the broad definition, with none of the cases meeting the Brighton Collaboration criteria for anaphylaxis. There were no severe allergic reactions with close temporal relation to the vaccine. However, one case of Type IV hypersensitivity in the Ad26.COV2.S group, which occurred 3 days after vaccination, was considered a related SAE by the investigator and Janssen (case does not meet the Brighton Collaboration Criteria for anaphylaxis). Refer to Table 23 in Appendix 12.4.

8.4.6.2 *Tinnitus*

Six cases of tinnitus were reported in the Ad26.COV2.S group and none in the placebo group. All these cases were considered nonserious. Review of the cases revealed no pattern in terms of temporal association with the vaccine (Time to onset range 1 to 22 days). All participants had underlying medical conditions (such as history of tinnitus and migraine, history of hypertension, seasonal allergies, and hypothyroidism) or used medications that offered a more plausible alternative cause for the event than the vaccine. None of these events have reported further complications such as hearing loss. In addition, there was only one case of tinnitus in the safety database from the AdVac platform (RSV program).

Details regarding the reported cases of tinnitus events are provided in Table 24 Appendix 12.4.

8.4.6.3 *Convulsions/Seizures*

Four cases were reported in the Ad26.COV2.S group (1 serious) and one case (non-serious) in the placebo group, all of which were considered not related to the study vaccine by the investigator. The serious case of convulsion/seizure was reported in a participant who received Ad26.COV2.S and had a history of epilepsy and obsessive-compulsive disorder that could have contributed to the event. One of the nonserious cases in the Ad26.COV2.S group was secondary to the SAE of transverse sinus thrombosis (see Section 8.4.3.3). Further review of the nonserious cases revealed no pattern in terms of temporal association with the vaccine (Time to onset range 8 to 41 days). For 3 of the 4 cases that occurred in the Ad26.COV2.S group, underlying medical conditions (such as dementia/epilepsy and diabetes) were present that may have contributed to the onset of the convulsive episode.

Details regarding the reported cases of convulsion/seizure events are provided in Table 25 in Appendix 12.4.

8.4.6.4 *Thrombotic and Thromboembolic Events*

The overall incidence of thrombotic and thromboembolic events (arterial and venous) was similar across Ad26.COV2.S (n=14, 0.1%) and placebo groups (n=10, <0.1%). Table 19 shows the distribution of thrombotic / thromboembolic events by subtype / organ class.

Table 19: Distribution of Thrombotic/Thromboembolic Events by Subtype/System Organ Class

Subtype/organ class	Ad26.COV2.S		Placebo	
	Serious	Nonserious	Serious	Nonserious
Deep Vein Thrombosis	4	5	2	1
DVT ¹	1	4	1	1
Pulmonary Embolism	3	1	1	0
Cerebrovascular events²	4 ³	0	2	1
Cardiovascular events	2	0	3	0
Gastrointestinal events	0	0	0	1
TOTAL (Cases)	9	5	7	3

¹ Includes one case reported as 'venous thrombosis of the limb' (non-serious)

² Includes one case of transverse sinus thrombosis that led to a study pause (see section 8.4.3.3)

³ Two events were reported in the same participant

A numerical imbalance was observed for the DVT/ PE subtype, with a total of 9 cases in the Ad26.COV2.S group (4 serious) and 3 cases in the placebo group (2 serious). Two of these cases were considered related to the study vaccine by the investigator: One nonserious AE of DVT reported with onset 27 days after vaccination with Ad26.COV2.S in a participant with a medical history of obesity and cholecystectomy and 1 SAE of DVT reported in the placebo group. Most of these participants had underlying medical conditions (such as obesity, hypothyroidism, diabetes) that may have contributed to the onset of these events.

Details regarding the reported cases of DVT are shown in Table 26 in Appendix 12.4 and case details of PE events are provided in Table 27 in Appendix 12.4.

8.4.6.5 *Demyelinating Disorders*

Four cases of demyelinating disorders were reported in the Ad26.COV2.S group (2 cases peripheral neuropathy, 1 benign monoclonal hypergammaglobulinemia, 1 Guillain-Barré syndrome) compared with 5 cases in the placebo group (2 cases peripheral neuropathy, 1 Guillain-Barré syndrome and 2 sensory loss). The case of Guillain-Barré syndrome in the Ad26.COV2.S group occurred 16 days after vaccination. The participant was hospitalized with worsening signs and symptoms of back and bilateral proximal lower extremity myalgias, horizontal diplopia, and mild headache. The SAE was ongoing for 29 days at the time of reporting and was reported as not resolved. The case was considered as indeterminate as per WHO AEFI criteria, however due to close temporal association and lack of other explanatory factors, it was considered as possibly related by Janssen for reporting purposes. Regarding the case of Guillain-Barré Syndrome in the

placebo group, the participant showed symptoms consistent with the prodromal phase of Guillain-Barré Syndrome before vaccination and therefore it was considered as unrelated.

8.4.6.6 *Bell's Palsy*

Three cases of Bell's palsy (facial paralysis) were reported in the Ad26.COV2.S group compared with two cases in the placebo group. Two cases of Bell's palsy in the Ad26.COV2.S group were considered related SAEs by the investigator, but unrelated by Janssen based on the participant's underlying medical conditions (diabetes, hypertension, obesity). The observed frequency of reported Bell's palsy in the Ad26.COV2.S group is consistent with the expected background rate in the general population, and there is no clear basis to conclude a causal relationship at this time.

8.4.7 *Adverse Events in Subgroups*

Ad26.COV2.S at a dose level of 5×10^{10} vp has an acceptable reactogenicity profile in participants ≥ 18 years of age. Overall, no clinically relevant differences in the reactogenicity profile of Ad26.COV2.S were observed across sex, race/ethnicities, geographies, comorbidities, SARS-CoV-2, or HIV serostatus at baseline. The frequency of solicited local and systemic AEs was lower in participants aged ≥ 60 years compared to participants aged ≥ 18 to < 60 years. No overall differences in safety were observed between older adults ≥ 65 years and ≥ 75 years of age and younger adults (≥ 18 to < 60 years of age), since similar frequencies of AEs were observed between the Ad26.COV2.S group and the placebo group within each age group. Furthermore, participants with one or more comorbidity (ie, asthma, cerebrovascular disease, chronic kidney disease, COPD, serious heart conditions, hypertension, and obesity) at baseline had higher frequencies of solicited AEs in the Ad26.COV2.S group compared to placebo.

8.5 **Safety Profile of AdVac® Platform**

The safety profile of Ad26.COV2.S is further supported by data from $> 193,000$ individuals who have been exposed to Janssen's AdVac®-based vaccines in the context of clinical studies and programs (cutoff: 21 December 2020). See Table 28 in Appendix 12.5 for a comprehensive overview of the AdVac clinical exposure and safety experience. The Adenoviral Vaccine Safety Database V5.0 (10 April 2020) includes pooled safety data of 26 completed Ad26-based vaccine studies, in which 4,874 participants (including adults and children) received at least one dose of an Ad26-based vaccine. The minimum duration for safety follow-up was 6 months post last vaccination and for some studies that included a long-term extension phase, the follow-up duration was up to 4.5 years. Post-vaccination reactogenicity after administration of Ad26-based vaccines consisted of mild to moderate AEs, including injection site reactions, malaise, fatigue, headache, and myalgia. Most solicited local AEs started 1 to 2 days after vaccination and resolved within 1 to 3 days. The majority of solicited systemic AEs started between 1 to 2 days after vaccine administration and resolved in 1 to 2 days.

In addition to information from healthy younger adults, the AdVac Safety Database also contains safety information from the following populations which were included in the Janssen Ad26-based vaccine studies across the different disease areas:

- Children have been included in a Phase 2 and a Phase 3 study of the Ebola vaccine development program. A total of 839 participants were included in these studies, of which 650 participants (254 aged 12 to 17 years, 252 aged 4 to 11 years and 144 aged 1 to 3 years) received the Ad26.ZEBOV (5×10^{10} vp) vaccine as dose 1 of the heterologous Ebola vaccine regimen (Ad26.ZEBOV, MVA-BN-Filo regimen) and a total of 189 participants received the control regimen (placebo [N=45] or active control [MenACWY; N=144]). Overall, no safety concerns have been raised to date in this population. No deaths, SAEs considered related to study vaccine or AEs leading to discontinuation were reported in pediatric participants.
- Participants aged ≥ 60 years have been included in a Phase 1 and a Phase 2a study of the RSV vaccine clinical development program. In total, 228 participants aged ≥ 60 years received an Ad26.RSV.preF-based regimen in these studies. Overall, no safety concerns have been raised to date in this population.
- HIV-infected adults have been included in two Phase 2 studies of the Ebola vaccine development program and one Phase 1 study of the HIV vaccine program. A total of 220 HIV-infected adults received the Ad26.ZEBOV, MVA-BN-Filo regimen and 17 received an Ad26.Mos.HIV vaccine regimen. Overall, no safety concerns have been raised to date in this population. There were no notable differences with regard to the safety profile of the Ad26-based vaccine regimens between HIV-infected and healthy adult participants.
- A pregnancy review included pregnancy cases reported from ongoing and completed Ad26-vectored vaccine trials for COVID-19 vaccine, Ebola vaccine, HIV vaccine, HPV vaccine, Filovirus vaccine, RSV vaccine and Zika vaccine cumulatively through 31 December 2020. It is worthwhile noting that the Ebola vaccine is currently given to pregnant women in context of a large-scale vaccination study EBL3008 (DRC vaccination campaign). In total 20,432 subjects have been enrolled in this study and 1,061 pregnancy cases were reported. In addition, a clinical study focused on vaccination of pregnant women with the Ebola vaccine is ongoing in Rwanda (N=2,000; 47 enrolled).
 - A total of 1,631 reported pregnancies were reviewed in this analysis. Of these 1,631 pregnancies, 1,522 reported exposure to Ebola vaccine or placebo in Ebola program, 101 reported exposure to HIV vaccine or placebo in HIV program and 8 reported exposure to COVID-19 vaccine or placebo in COVID-19 program. None of the cases reported exposure to HPV vaccine, RSV vaccine, Filovirus vaccine, or Zika vaccine.
 - Of the 1,522 pregnancies reported from the Ebola vaccine trials with reported exposure to Ad26.ZEBOV vaccine, most cases were reported in VAC52150EBL3008 with 1,062 reported pregnancies. In this study, conducted in DRC, pregnancy is not an exclusion criterion for vaccination and pregnant women could be vaccinated with Ad26.ZEBOV throughout all 3 trimesters. In addition,

there were no contraceptive requirements in this study as these subjects were considered at high risk for Ebola disease that outweighed the potential risk of vaccination during pregnancy or near conception.

- Spontaneous abortion was reported in 5.8% (88/1,522) of pregnancies, whereas all other types of abortions (ie, induced abortion [6], elective abortion [5], abortion, abortion incomplete and incomplete abortion [each reported once]) were reported in 0.9% (14/1,522) of pregnancies. Congenital malformations reported in 3 cases were lingula frenulum, cleft lip and evisceration on exomphalos, none of which were considered related to the study vaccine. In addition, none of the reported adverse pregnancy outcomes and SAEs was considered related to the study vaccine.
- Of the 101 pregnancies reported from the HIV vaccine trials with exposure to Ad26.Mos4.HIV candidate vaccine, the most frequently reported study protocol was VAC89220HPX2008 with 90 reported pregnancies. In this study, only women are recruited. Spontaneous abortion was reported in 12.9% (13/101) and elective abortion in 3% (3/101) pregnancies. None of the pregnancies reported any congenital malformations. None of the reported adverse pregnancy outcomes and SAEs were considered related to the study vaccine.
- All 8 pregnancies reported from COVID-19 vaccine trials were from protocol VAC31518COV3001. There was 1 case each for spontaneous abortion and elective abortion. None of the pregnancies reported any congenital malformations. None of the reported adverse pregnancy outcomes and SAEs were considered related to the study vaccine.
- The reported spontaneous abortion rates are within the expected abortion rates during pregnancy which could range anywhere from 10% to 30% [61].
- For the Ebola vaccine, a study, focused on safety and immunogenicity in pregnant women is currently ongoing in Rwanda (N= 47; cutoff: 21 Dec 2020), including follow-up of the newborns, and the vaccinated and non-vaccinated control mothers.

These data indicate that, overall, the Ad26-based vaccines have an acceptable safety and reactogenicity profile, without significant safety issues identified to date. In addition, the review of the available pregnancy data is not suggestive of a pregnancy-related safety concern.

8.6 Additional Safety Data: Other Ongoing Clinical Studies

In general, the safety profile observed in the Phase 3 study COV3001 is consistent with the safety profile observed in the Phase 1 and 2 studies (COV1001, COV1002, and COV2001) and the Phase 3 study COV3009. Longer-term results from these studies (with the longest median follow-up time being in study COV1001: 166 and 144 days for adults ≥ 18 to ≤ 55 and ≥ 65 years of age, respectively) further support the acceptable safety profile for Ad26.COV2.S. Up to the cut-off date of 11 January 2021 (COV1001, COV1002, and COV2001) and 14 January 2021 (COV3009), one

death (participant shot and killed in a homicide) was reported in study COV3009 and a total of 26 participants reported one or more SAEs. Of these 26 participants, 2 participants reported a total of 2 SAEs considered to be related to the study vaccine: Grade 3 pyrexia and Grade 2 multiple sclerosis however based on imaging findings the event of multiple sclerosis was assessed by an expert neurologist as likely chronic in origin and preceding vaccination and therefore considered unrelated by Janssen. Early discontinuations of vaccination or study due to (S)AEs were infrequent in all groups.

9 PHARMACOVIGILANCE/SAFETY MONITORING PLAN

Janssen has drafted a comprehensive pharmacovigilance plan to identify potential risks and procedures for collecting and evaluating ongoing clinical safety data relevant to the use of Ad26.COV2.S.

9.1 Routine Pharmacovigilance

Janssen will follow standard routine pharmacovigilance (PV) processes with regard to Ad26.COV2.S, along with the additional actions referenced in the PV plan.

- **Safety reporting.** Spontaneous and solicited reports, including any SAEs (regardless of attribution to vaccination), COVID-19 disease resulting in hospitalization or death, vaccination administration errors and Multisystem Inflammatory Syndrome will be submitted to Vaccine Adverse Event Reporting System (VAERS) within 15 calendar days.
- **Active follow-up.** A plan for active follow-up of all AEs, including SAEs among individuals who received Ad26.COV2.S under the EUA has been developed including phone call attempts to the reporter or healthcare provider, as appropriate.
- **Standard/passive follow-up.** Individual Case Safety Reports will be followed up promptly to obtain additional information relevant to the report as necessary to provide a complete description of the safety event. Two follow-up attempts are performed for all ICSRs and a standard vaccine AE follow-up questionnaire will be generated for all case follow-up. Additionally, an adverse event of special interest (AESI) list has been created, for which questions will be added to the standard vaccine AE follow-up questionnaire on a case-by-case basis. Targeted follow-up questionnaires will be used to collect follow-up information on reports of anaphylaxis and COVID-19 vaccine failure/VAED, including VAERD.
- **Periodic aggregate review of safety data.** Following FDA guidance, Janssen will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data.
- **Literature review.** Literature monitoring for Ad26.COV2.S includes both an automated daily search for published and pre-publication/online first references in commercial database products as well as a manual review. References retrieved by the search strategies are reviewed by a healthcare professional and are escalated based on reporting of either new safety observations or new aspects of known risks that require further assessment.
- **Signal investigation.** All available safety information across clinical investigations, post-marketing data, and all other sources of information is reviewed on a regular basis. Routine aggregate signal detection will include regular surveillance of AE reports received in Janssen's Global Safety Database. Additional reviews will be performed in external databases such as VAERS, WHO VigiBase and EudraVigilance.

9.2 Additional PV Activities

Additional PV activities include data collection from both ongoing and planned interventional clinical studies and active surveillance studies, including:

- **Interventional Studies**

- Long-term safety data, as collected in ongoing studies COV3001 and COV3009, for 2 years in the post-authorization safety study in the US and for 1 year in the post-authorization safety study in Europe.
- For consenting participants in the US, utilization of tokenization and matching procedures for exploratory analysis of participant's medical data prior to, during, and following participation in the study (real-world data). Analysis will be performed to relate real-world data to vaccine immune responses, efficacy and duration of protection, and AEs.
- COV2001 – A randomized, double-blind, placebo-controlled study to evaluate a two dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive.
- COV3006 – A randomized, double-blind, placebo-controlled study to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a two-dose regimen followed by a booster in healthy children from birth to 17 years inclusive.
- COV2004 – Assessment of the safety and immunogenicity of Ad26.COV2.S in pregnant women and their offspring.
- A coadministration study of Ad26.COV2.S with seasonal influenza vaccine.
- Use in immunocompromised participants.

- **Non-Interventional Studies**

- Post-authorization, observational study to assess the safety of Ad26.COV2.S in the US: this study is an active surveillance activity conducted in large US health insurance claims and/or electronic health record (EHR) database(s) to retrospectively assess the occurrence of pre-specified AESIs within specific risk periods following administration of the vaccine in the framework of the national immunization program.
- Post-authorization, observational, COVID-19 vaccine pregnancy exposure registry. This is a multi-country study including the US. This prospective cohort study is designed to assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.
- Post-authorization, observational study to assess the safety of Ad26.COV2.S in Europe: this study is a multi-country active surveillance activity conducted in European EHR databases. The study aims at retrospectively assessing the

occurrence of pre-specified AESIs within specific risk periods following administration of the vaccine in the framework of the national immunization programmes.

- Post-authorization, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe. This is a multi-country, observational, prospective hospital-based study, following a test-negative design to assess the vaccine effectiveness in preventing laboratory-confirmed SARS-CoV-2 hospitalizations up to 2 years post-vaccination.

Key Efficacy Assessments

Key efficacy assessments include the surveillance for COVID-19 like signs and symptoms, recording of COVID-19-related hospitalizations and complications, and the laboratory confirmation of SARS-CoV-2 infection by a molecular assay (based on RT-PCR) and by anti-SARS-CoV-2 serology. Immunogenicity assessments, and especially assessments of the humoral immune responses with emphasis on neutralizing and binding antibodies will also be performed.

Key Safety Assessments

Key safety assessments will include the monitoring of solicited and unsolicited AEs (in the Safety Subset only), and the collection of SAEs and MAAEs in all participants. The viral load of SARS-CoV-2 will be assessed in confirmed COVID-19 cases. Biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity will also be studied. Additionally, MRU will be recorded for all participants with molecularly confirmed, symptomatic COVID-19.

Additional characteristics related to current work situation, living situation, and community interactions will be collected for risk factor analysis, if allowed per local regulations. Participants who consent to this will be interviewed on these aspects prior to vaccination on Day 1 and, at other timepoints, on changes compared to Day 1. For consenting participants in the US, medical data (electronic health records, claims and laboratory data from other care settings) from 5 years prior to study enrolment until 5 years after study completion may be accessed utilizing tokenization and matching procedures (ie, the generation of anonymous identifiers or “tokens” [hashed and encrypted combinations of identifying elements] to allow linking of participant data from different sources without compromising the participant’s confidentiality).

Exploratory Analyses

These data together with data collected as part of the study as specified in the Schedules of Activities, may be used for exploratory analyses to enhance our understanding of the impact or prior medical history on the response to immunization and the impact of immunization on efficacy and duration of efficacy as well as AEs that may occur during and after completion of the study. The statistical analyses will be described in detail in the SAP.

10 BENEFIT-RISK CONCLUSIONS

The efficacy, immunogenicity and safety data presented in this briefing document support a favorable benefit-risk profile for Ad26.COVS.2 in the proposed EUA indication, ie, single-dose active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults ≥ 18 years of age.

10.1 Efficacy

In the pivotal efficacy and safety study COV3001, a total of 21,895 participants received Ad26.COVS.2 and 21,888 participants received placebo. Importantly, the timing and multiple settings of the COV3001 study allowed Janssen to assess VE against COVID-19 caused by different SARS-CoV-2 variants as well as VE against COVID-19 early after vaccination in a situation of very high SARS-CoV-2 transmission rates. Janssen performed the primary analysis as soon as the required 2-month (8 weeks) median follow-up was reached.

Vaccine efficacy (adjusted 95% CI) against molecularly confirmed moderate to severe/critical COVID-19 occurring at least 14 days and at least 28 days after a single Ad26.COVS.2 dose in participants who were seronegative at the time of vaccination was 66.9% (59.03; 73.40) and 66.1% (55.01; 74.80), respectively.

VE (adjusted 95% CI) against molecularly confirmed severe/critical COVID-19 occurring at least 14 days and 28 days after a single Ad26.COVS.2 dose was 76.7% (54.56; 89.09) and 85.4% (54.15; 96.90), respectively. There was an observed vaccine effect on preventing COVID-19 that required medical intervention and on preventing all-cause mortality. The onset of efficacy against severe/critical COVID-19 was evident as early as 7 days after a single dose, with a clear trend for increasing VE which persisted for the current duration of follow-up (median 58 days).

Vaccine efficacy against all symptomatic molecularly confirmed COVID-19, as measured by a severity-adjusted weighted analysis (BOD) including mild, moderate and severe/critical COVID-19, was 68.1% (60.26; 74.32) and 69.0% (56.68; 77.64), occurring at least 14 days and at least 28 days after a single Ad26.COVS.2 dose, respectively. Given the limited number of mild COVID-19 cases, VE against any symptomatic COVID-19 was consistent with the co-primary endpoints measuring VE against moderate to severe/critical COVID-19.

With 34.6% of participants being ≥ 60 years of age in COV3001, Ad26.COVS.2 showed consistent efficacy across age groups (≥ 60 and ≥ 18 to < 60 years of age), against moderate to severe/critical COVID-19, as well as against severe/critical COVID-19. Analyses of vaccine efficacy in elderly participants with or without comorbidities may be confounded by small numbers and differences in follow-up time.

Preliminary data, based on a limited number of Day 71 results, suggest a vaccine effect against asymptomatic or undetected infection. This finding needs to be further investigated with additional data.

Ad26.COV2.S VE was consistent between sexes, and between Hispanic, non-Hispanic, Black/African American and White participants. For some of the other racial subgroups, the findings were variable and therefore, as the study continues, additional follow-up data will be gathered to better understand VE in some of the races. Across regions, VE against moderate to severe/critical COVID-19 with onset at least 14 days and at least 28 days after vaccination VE ranged from 52.0% to 74.4%.

In the US, VE (95% CI) against moderate to severe/critical COVID-19 (including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation) was 74.4% (65.00; 81.57) and 72.0% (58.19; 81.71), when considering cases from at least 14 days and at least 28 days after vaccination, respectively. Vaccine efficacy (95% CI) against severe/critical COVID-19 in the US was 78.0% (33.13; 94.58) at least 14 days and 85.9% (-9.38; 99.69) at least 28 days after vaccination. Preliminary sequence data confirm that approximately 96% of the centrally confirmed COVID-19 cases were due to the D614G variant and approximately 3% were due to the CAL.20C variant.

In South Africa, high efficacy was observed against severe/critical COVID-19 and robust VE was observed for moderate to severe/critical COVID-19. This is especially important since preliminary sequence data confirm that approximately 96% of the COVID-19 cases that occurred in the study in South Africa were due to the SARS-CoV-2 variant 20H/501Y.V2 (belonging to the B.1.351 lineage), implying that Ad26.COV2.S is efficacious against this newly emerging and rapidly spreading strain. Vaccine efficacy (95% CI) against severe/critical COVID-19 (including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation) was 73.1% (40.03; 89.36) at least 14 days after vaccination and increased to 81.7% (46.18; 95.42) at least 28 days after vaccination. An effect was also seen on mortality, since all COVID-19-associated deaths in the study in South Africa, occurred in participants in the placebo group. Vaccine efficacy (95% CI) against moderate to severe/critical COVID-19 (including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation) was 52.0% (30.26; 67.44) at least 14 days and 64.0% (41.19; 78.66) at least 28 days after vaccination. The high VE against severe/critical COVID-19 observed in South Africa is reassuring since it can be expected that the SARS-CoV-2 variant 20H/501Y.V2 will further spread globally over time.

In Brazil, VE estimates were higher than those in South Africa and similar to those in the US. Preliminary sequence data confirm that approximately 71% of the COVID-19 cases in the study that occurred in Brazil appeared to be due to a variant from the P.2 lineage. This implies that efficacy in Brazil is not impacted by the high prevalence of the variant of the P.2 lineage as it is quite similar to the VE observed in the US, where D614G is highly prevalent (see Table 2).

Participants from the Ad26.COV2.S group with moderate COVID-19 reported fewer and less severe COVID-19 symptoms than participants from the placebo group with moderate COVID-19.

10.2 Immunogenicity

A single dose of Ad26.COV2.S elicited a SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 Spike binding antibody response that is detected by Day 15, increases to Day 57 and is maintained until at least Day 85 across age groups and shows signs of maturation. Cellular responses to Ad26.COV2.S were detected in the vast majority of participants at Day 15 and consisted of CD8+ T cell responses as well as CD4+ T cell responses, predominantly the Th1 phenotype.

There is currently no indication of significant waning of immune responses up to at least Day 85. These results are consistent with immune responses and durability observed with the Ad26-vector platform data and with nonclinical data with Ad26.COV2.S showing maintenance of protective immunity for 6 months.

10.3 Safety

Ad26.COV2.S, given as a single dose, is found to have an acceptable safety and reactogenicity profile in adults ≥ 18 years of age and did not raise safety concerns in any of the assessed populations that are reflective of the target groups for vaccination, including adults ≥ 60 years of age and adults with comorbidities (including comorbidities associated with an increased risk of progressing to severe/critical COVID-19).

Clinical data with a single dose of Ad26.COV2.S did not indicate any evidence of VAED, including VAERD, which confirms the nonclinical observations that the theoretical risk of VAERD is low.

There were more cases of tinnitus, convulsions/seizures, and PE/DVT in the Ad26.COV2.S group compared to placebo. However, in the majority of the cases, the participants had one or more underlying medical conditions that are known risk factors for the event in question or used medications that offered a more plausible alternative cause for the event than the vaccine. In the absence of any signal in the AdVac safety database for these events of interest and given that the total number of cases observed in the study is low and within the rates observed in the general population, Janssen does not consider these events as causally related to the vaccine.

10.4 Conclusion

The SARS-CoV-2 outbreak constitutes a public health emergency of international concern. There is an urgent medical need for effective and safe COVID-19 vaccines to help control the pandemic. The high rates of mortality and hospitalizations related to COVID-19 result in a large burden on the individual affected, health care systems globally, and society in general.

Knowing that a single dose regimen has major advantages when used during an outbreak that requires mass vaccination campaigns, Janssen's aim was to evaluate whether a single dose regimen of its Ad26.COV2.S vaccine candidate could play a valuable role. Recent modelling results suggest that a single dose COVID-19 vaccine can support faster vaccine uptake in a population than a two-dose vaccine, which may result in preventing more disease and preventing more deaths [62].

The results presented in this document demonstrate that (1) a single dose of Ad26.COV2.S is effective against symptomatic COVID-19, (2) a single dose of Ad26.COV2.S is highly effective in the prevention of severe/critical COVID-19, particularly in prevention of hospitalization and death, across all countries, and ages; and (3) a single dose of Ad26.COV2.S is highly effective against severe/critical COVID-19 caused by newly emerging strains, such as the 20H/501Y.V2 variant first observed in South Africa and the P.2 variant first observed in Brazil. This finding is especially reassuring since it can be expected that more variants will occur over time. Use of Ad26.COV2.S could thus help to control the pandemic, reduce the burden of disease and relieve pressure on the health care infrastructure. In addition, Ad26.COV2.S can be stored for at least 3 months at normal refrigerator temperatures of 2° C to 8° C (36° F to 46° F), and its shipping and storage fits into the existing medical supply infrastructure. These conditions will simplify deployment of vaccination.

Ad26.COV2.S has an acceptable safety and reactogenicity profile. These results are further substantiated by the long-term and robust platform data demonstrating an acceptable long-term safety and reactogenicity profile and durable immune responses for the Ad26-based vaccines. The known and potential benefits of Ad26.COV2.S outweigh the known and potential risks.

Janssen commits to a comprehensive pharmacovigilance plan to identify potential risks and procedures for collecting and evaluating ongoing clinical safety data relevant to the use of Ad26.COV2.S.

The efficacy, immunogenicity and safety data presented in this application support a favorable benefit-risk profile for Ad26.COV2.S in the proposed EUA indication, ie, active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults ≥ 18 years of age.

In conclusion, in outbreak situations, where mass vaccination programs are needed, a single dose regimen, offering early onset of protection can play a critical role. Based on the high efficacy shown in study COV3001, especially with regard to prevention of severe disease and death, the Ad26.COV2.S vaccine is well positioned to address this need.

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12 APPENDICES

12.1 Appendix: Enrollment Criteria for Phase 3 Study COV3001 (ENSEMBLE)

Provided below are the complete enrollment criteria that were used to determine the eligibility of possible participants to take part in the Phase 3 study COV3001.

Inclusion Criteria

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

1. Criterion modified per Amendment 1:
 - 1.1 Participants must provide consent indicating that he or she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.
2. Participant is willing and able to adhere to the prohibitions and restrictions specified in this protocol.
3. **Stages 1a and 1b:** Participant is ≥ 18 to < 60 years of age on the day of signing the ICF.
Stages 2a and 2b: Participant is ≥ 60 years of age on the day of signing the ICF.
4. Criterion modified per Amendment 1:
 - 4.1. Criterion modified per Amendment 2:
 - 4.2 Criterion modified per Amendment 3:
 - 4.3 **Stages 1a and 2a:** In the investigator's clinical judgement, participant must be either in good or stable health, including a BMI < 30 kg/m².

Participants may have underlying illnesses (not associated with increased risk of progression to severe COVID-19² as specified in Exclusion Criterion 24), as long as their symptoms and signs are stable and well-controlled. If participants are on medication for a condition not part of the comorbidities listed in Exclusion Criterion 24, the medication dose cannot have been increased within 12 weeks preceding vaccination and expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and BMI measurement at screening.

Stages 1b and 2b: In the investigator's clinical judgement, participant may have a stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 as specified in Exclusion Criterion 24 (eg, stable/well controlled -HIV infection)*. If participants are on medication for a medical condition (including comorbidities associated with an increased risk of

²Per US CDC. In this study, former or current smoking/vaping and mild hypertension (according to the Toxicity Grading Scale in the protocol) will not be considered as a comorbidity. In addition, for this study gestational diabetes was deleted from the list since it is not applicable as no pregnant women are allowed to participate in the study.

progression to severe COVID-19), the medication dose cannot have been increased within 12 weeks preceding vaccination and must be expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and BMI measurement at screening.

* Stable/well-controlled HIV infection includes:

- a. Documented CD4 cell count ≥ 300 cells/ μL within 6 months prior to screening.
- b. Documented HIV viral load < 50 copies/mL within 6 months prior to screening.
- c. Participant must be on a stable anti-retroviral treatment (ART) for 6 months (unless the change is due to tolerability, in which case the regimen can be for only the previous 3 months; changes in formulation are allowed; nationwide guidelines that require transition from one ART regimen to another are allowed) and the participant must be willing to continue his/her ART throughout the study as directed by his/her local physician.

Note: Participants with ongoing and progressive comorbidities associated with HIV infection will be excluded but comorbidities associated with HIV infection that have been clinically stable for the past 6 months are not an exclusion criterion.

Laboratory methods for confirming a diagnosis of HIV infection are: Any evidence (historic or current) from medical records, such as ELISA with confirmation with Western Blot or PCR, or of a detectable viral load (country-specific regulatory approved tests). A laboratory result within 6 months of screening does not need to be repeated.

If a potential participant does not have HIV viral load and CD4 cell count data in his/her medical records from the last 6 months, they will be instructed to go to their local health care provider and obtain the necessary data for potential entry into the trial.

5. Criterion modified per Amendment 1:

5.1 Contraceptive (birth control) use should be consistent with local regulations regarding the acceptable methods of contraception³ for those participating in clinical studies.

Before randomization, participants must be either:

- a. Not of childbearing potential
- b. Of childbearing potential and practicing an acceptable effective method of contraception and agrees to remain on such a method of contraception from providing consent until 3 months after administration of study vaccine. Use of hormonal contraception should start at least 28 days before the administration of study vaccine. The investigator should evaluate the potential for contraceptive

³ Use of condoms is not considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms.

method failure (eg, noncompliance, recently initiated) in relationship to the vaccination. Acceptable effective methods for this study include:

1. hormonal contraception:
 - i. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
 - ii. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
2. intrauterine device;
3. intrauterine hormone-releasing system;
4. bilateral tubal occlusion/ligation procedure;
5. vasectomized partner (the vasectomized partner should be the sole partner for that participant);
6. sexual abstinence*.

Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from providing consent until 3 months after receiving study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

6. All participants of childbearing potential must:
 - a Have a negative highly sensitive urine pregnancy test at screening
 - b Have a negative highly sensitive urine pregnancy test on the day of and prior to study vaccine administration.
7. Participant agrees to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving the study vaccine.
8. Must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.
9. Must be able to read, understand, and complete questionnaires in the eCOA (ie, the COVID-19 signs and symptoms surveillance question, the e-Diary, and the electronic patient-reported outcomes (ePROs)⁴.

Exclusion Criteria

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

10. Participant has a clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature $\geq 38.0^{\circ}\text{C}$ (100.4°F) within

⁴ Participants with visual impairment are eligible for study participation and may have caregiver assistance in completing the eCOA questionnaires.

- 24 hours prior to the planned study vaccination; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.
11. Participant has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine).
 12. Criterion modified per Amendment 1:
 - 3.1 Criterion modified per Amendment 2:
 - 3.2 Criterion modified per Amendment 3:
 - 3.3 Participant has abnormal function of the immune system resulting from:
 - a. Clinical conditions (eg, autoimmune disease or potential immune mediated disease or known or suspected immunodeficiency, or participant on hemodialysis) expected to have an impact on the immune response of the study vaccine. Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator. Non-immunomodulator treatment is allowed as well as steroids at a non-immunosuppressive dose or route of administration.
 - b. Chronic or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥ 2 weeks of daily receipt of 20 mg of prednisone or equivalent.
Note: Ocular, topical or inhaled steroids are allowed.
 - c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of study vaccine and during the study.
 13. Criterion modified per Amendment 3:
 - 4.1 Participant received treatment with Ig in the 3 months or exogenous blood products (autologous blood transfusions are not exclusionary) in the 4 months before the planned administration of the study vaccine or has any plans to receive such treatment during the study.
 14. Participant received or plans to receive:
 - a. Licensed live attenuated vaccines – within 28 days before or after planned administration of study vaccine.
 - b. Other licensed (not live) vaccines – within 14 days before or after planned administration of study vaccine.
 15. Participant previously received a coronavirus vaccine.
 16. Criterion modified per Amendment 1:

- 7.1 Criterion modified per Amendment 2:
- 7.2 Criterion modified per Amendment 3:
- 7.3 Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19) within 30 days or used an invasive investigational medical device within 30 days or received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study.

Note: Participation in an observational clinical study is allowed at the investigator's discretion; please notify the sponsor (or medical monitor) of this decision.

Efforts will be made to ensure inclusion of participants who have not been previously enrolled in coronavirus studies and to prevent participants from subsequently enrolling in other coronavirus studies during their participation in this study.

The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination (see also Exclusion Criterion 15) and during the study, except under the conditions described in the protocol.

17. Criterion modified per Amendment 1:
 - 8.1 Participant is pregnant or planning to become pregnant within 3 months after study vaccine administration.
18. Participant has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
19. Participant has a contraindication to IM injections and blood draws, eg, bleeding disorders.
20. Criterion deleted per Amendment 1:
21. Criterion modified per Amendment 1:
 - 12.1 Participant has had major psychiatric illness which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.
22. Participant cannot communicate reliably with the investigator.
23. Participant who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.
24. Criterion modified per Amendment 1:
 - 15.1 Criterion modified per Amendment 2:

15.2 Stages 1a and 2a:

- Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19⁵, ie, participants with moderate to severe asthma; chronic lung diseases such as COPD (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension; moderate to severe high blood pressure; obesity (body mass index [BMI] ≥ 30 kg/m²); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; and sleep apnea.
 - Participants with a history of or current Parkinson's disease; seizures; ischemic strokes; intracranial hemorrhage; encephalopathy and meningoencephalitis.
25. **Stages 1a and 2a:** Participant has a history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence).
26. Criterion Modified per Amendment 2:
- 17.1 Participant has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).
27. **Stages 1a and 2a:** Participant had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization, or has surgery requiring hospitalization planned during the time the participant is expected to participate in the study or within 6 months after study vaccine administration.
28. **Stages 1a and 2a:** Participant has chronic active hepatitis B or hepatitis C infection per medical history.

⁵Per US CDC. In this study, former or current smoking/vaping and mild hypertension (according to the Toxicity Grading Scale in the protocol) will not be considered as a comorbidity. Gestational diabetes was deleted from the list since it is not applicable as no pregnant women are allowed to participate in the study.

12.2 Appendix: Additional Demographics

Table 20: Additional Global Baseline Demographics and Comorbidities (Study COV3001)

Full Analysis Set (FAS)	Ad26.COV2.S N=21,895		Placebo N=21,888	
	n	%	n	%
Age Group				
18-59	14564	66.5%	14547	66.5%
18-39	5031	23.0%	5014	22.9%
40-59	9533	43.5%	9533	43.6%
≥60	7331	33.5%	7341	33.5%
60-69	5224	23.9%	5362	24.5%
70-79	1893	8.6%	1762	8.1%
≥80	214	1.0%	217	1.0%
≥65	4259	19.5%	4302	19.7%
≥75	809	3.7%	732	3.3%
≥1 Comorbidity	8936	40.8%	8922	40.8%
Obesity	6277	28.7%	6215	28.4%
Hypertension	2225	10.2%	2296	10.5%
Type 2 Diabetes Mellitus	1600	7.3%	1594	7.3%
Serious heart conditions	497	2.3%	511	2.3%
Asthma	262	1.2%	300	1.4%
COPD	231	1.1%	206	0.9%
Cancer	112	0.5%	114	0.5%
Chronic Kidney Disease	112	0.5%	118	0.5%
Liver Disease	103	0.5%	103	0.5%
Type 1 Diabetes Mellitus	105	0.5%	90	0.4%
Cerebrovascular Disease	78	0.4%	80	0.4%
Neurologic conditions	82	0.4%	125	0.6%
ICP from blood transplant	43	0.2%	36	0.2%
Sickle Cell Disease	13	0.1%	5	<0.1%
Thalassemia	16	0.1%	30	0.1%
Cystic Fibrosis	1	<0.1%	3	<0.1%
ICP from organ transplant	7	<0.1%	3	<0.1%
Pulmonary Fibrosis	10	<0.1%	9	<0.1%

Table 21: Additional US Baseline Demographics and Comorbidities (Study COV3001)

US Subgroup	Ad26.COV2.S n=9,655		Placebo n=9,647	
	n	%	n	%
Full Analysis Set (FAS)				
Age Group				
18-59	5894	61.0%	5870	60.9%
18-39	1836	19.0%	1834	19.0%
40-59	4058	42.0%	4036	41.9%
≥60	3761	39.0%	3777	39.1%
60-69	2580	26.7%	2627	27.2%
70-79	1060	11.0%	1026	10.6%
≥80	121	1.3%	124	1.3%
≥65	2299	54.0%	2369	55.1%
≥75	445	55.0%	416	56.8%
≥1 Comorbidity	4227	43.8%	4247	44.0%
Obesity	3085	32.0%	3054	31.7%
Hypertension	1139	11.8%	1166	12.1%
Type 2 Diabetes Mellitus	743	7.7%	729	7.6%
Serious heart conditions	291	3.0%	304	3.2%
Asthma	160	1.7%	203	2.1%
COPD	140	1.5%	131	1.4%
Cancer	82	0.8%	89	0.9%
Chronic Kidney Disease	69	0.7%	84	0.9%
Neurologic conditions	60	0.6%	84	0.9%
Liver Disease	54	0.6%	44	0.5%
Cerebrovascular Disease	48	0.5%	41	0.4%
Type 1 Diabetes Mellitus	45	0.5%	34	0.4%
ICP from blood transplant	26	0.3%	21	0.2%
Thalassemia	8	0.1%	17	0.2%
Pulmonary Fibrosis	5	0.1%	5	0.10%
Sickle Cell Disease	8	0.1%	3	<0.1%
ICP from organ transplant	3	<0.1%	2	<0.1%
Cystic Fibrosis	1	<0.1%	1	<0.1%

12.3 Appendix: Additional Efficacy Displays

Table 22: Vaccine Efficacy Against Moderate to Severe/Critical and Severe/Critical COVID-19 by Country, with Absolute Case Numbers (Per Protocol Population)

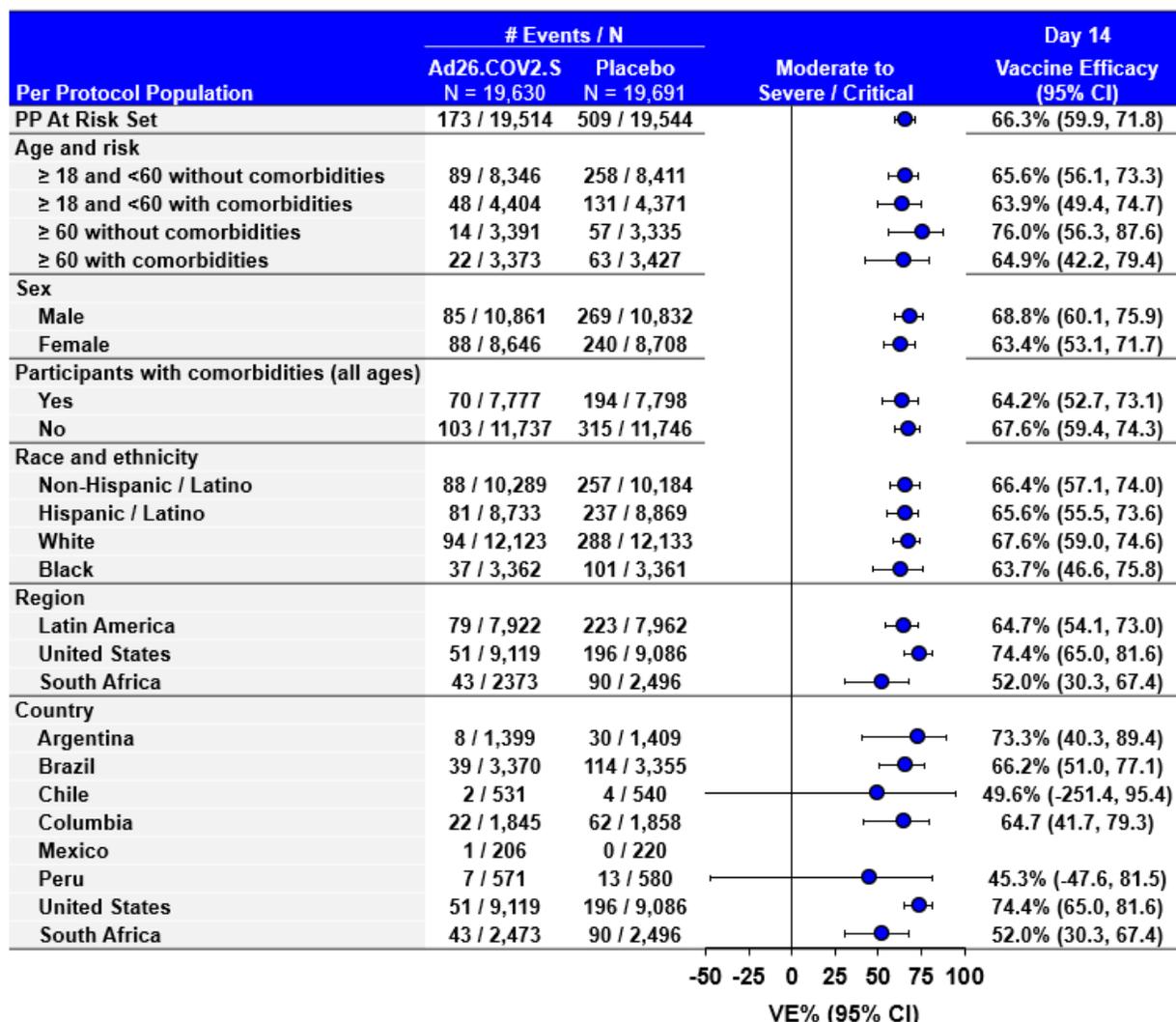
PCR+ by central laboratory ^a							
Country	Onset	Severity					
		Absolute Cases		Moderate to Severe/Critical Point Estimate (95% CI)	Absolute Cases		Severe/Critical Point Estimate (95% CI)
		Ad26.	Placebo		Ad26.	Placebo	
Global	≥14 days after vaccination	116	348	66.9% (59.0, 73.4)*	14	60	76.7% (54.6, 89.1)*
	≥28 days after vaccination	66	193	66.1% (55.0, 74.8)*	5	34	85.4% (54.2, 96.9)*
PCR+ from any source ^b							
Country	Onset	Severity					
		Absolute Cases		Moderate to Severe/Critical Point Estimate (95% CI)	Absolute Cases		Severe/Critical Point Estimate (95% CI)
		Ad26.	Placebo		Ad26.	Placebo	
Global	≥14 days after vaccination	173	509	66.3% (59.9, 71.8)*	19	80	76.3% (57.9, 87.5)*
	≥28 days after vaccination	113	324	65.5% (57.2, 72.4)*	8	48	83.5% (54.2, 96.9)*
US	≥14 days after vaccination	51	196	74.4% (65.0, 81.6)	4	18	78.0% (33.1, 94.6)
	≥28 days after vaccination	32	112	72.0% (58.2, 81.7)	1	7	85.9% (-9.4, 99.7)
Brazil	≥14 days after vaccination	39	114	66.2% (51.0, 77.1)	2	11	81.9% (17.0, 98.1)
	≥28 days after vaccination	24	74	68.1% (48.8, 80.7)	1	8	87.6% (7.8, 99.7)
South Africa	≥14 days after vaccination	43	90	52.0% (30.3, 67.4)	8	30	73.1% (40.0, 89.4)
	≥28 days after vaccination	23	64	64.0% (41.2, 78.7)	4	22	81.7% (46.2, 95.4)

*Adjusted 95% CI

^a Analysis based on a data set of centrally confirmed COVID-19 cases.

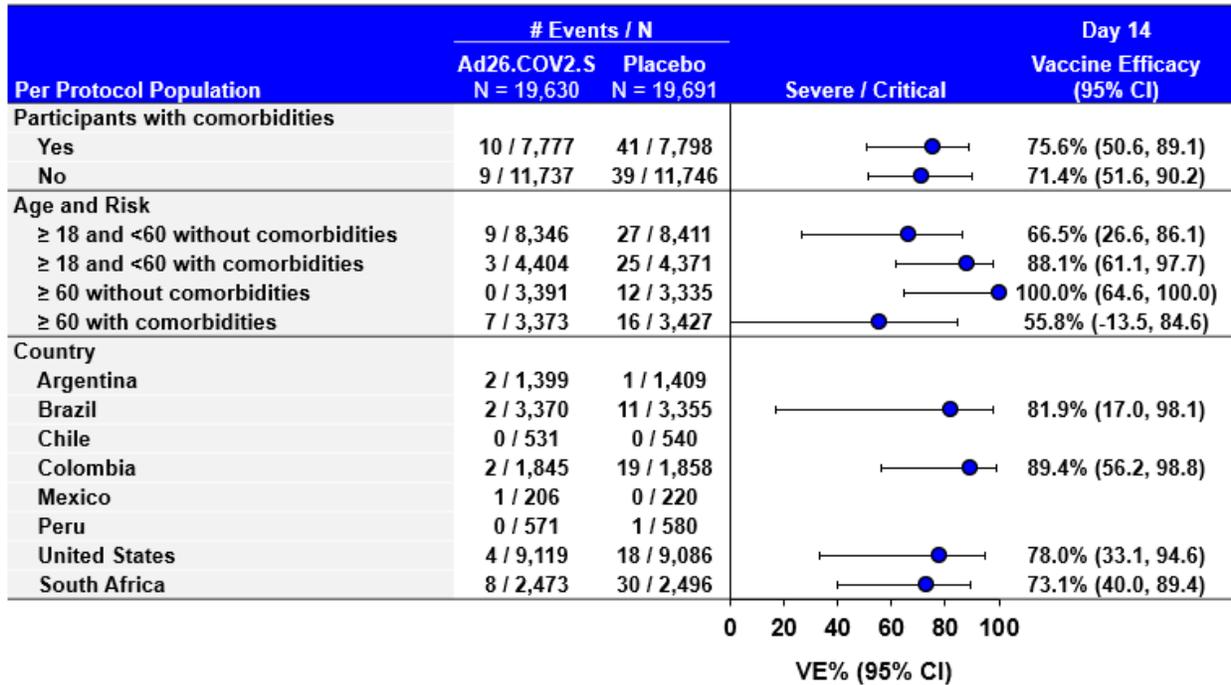
^b Analysis based on a data set including all COVID-19 cases with a positive PCR from any source, regardless of central confirmation.

Figure 24: Vaccine Efficacy Against Moderate to Severe/Critical COVID-19 from at Least 14 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001)



Note: Includes cases with a positive PCR from any source, regardless of central confirmation
Some subgroups have small numbers, reflected by the wide confidence intervals.

Figure 25: Vaccine Efficacy Against Severe/Critical COVID-19 from at Least 14 Days After Vaccination by Demographic and Baseline Characteristics, Per Protocol Population (Study COV3001)



Note: Includes cases with a positive PCR from any source, regardless of central confirmation
Some subgroups have small numbers, reflected by the wide confidence intervals.

12.4 Appendix: Adverse Events of Interest

Table 23: Adverse Events of Interest: Hypersensitivity (Study COV3001)

Study Group	Age/Sex	Preferred Term	Serious?	Time to Event (Days)	Outcome	Relationship (PI)	Case notes
Ad26.Cov2.S	20/F	Drug hypersensitivity	No	2	Recovered	Not Related	Allergic reaction to dipyrone
Ad26.Cov2.S	49/M	Drug eruption	No	36	Recovered	Not Related	Skin rash from unknown medication
Ad26.Cov2.S	48/M	Drug hypersensitivity	No	16	Not Recovered	Not Related	Allergic reaction to aspirin
Ad26.Cov2.S	61/F	Hypersensitivity	No	41	Recovering	Not Related	Hypersensitivity - cause unknown
Ad26.Cov2.S	34/M	Hypersensitivity	No	11	Recovered	Not Related	Hypersensitivity (allergic rhinitis)
Ad26.Cov2.S	45/F	Hypersensitivity	No	15	Recovered	Related	Unusual allergy symptoms (poss. Delayed hypersensitivity)
Ad26.Cov2.S	47/M	Hypersensitivity	No	5	Recovering	Not Related	Allergic reaction allergies - cause unknown
Ad26.Cov2.S	48/F	Hypersensitivity	No	7	Recovered	Not Related	Allergies
Ad26.Cov2.S	42/M	Vaccination site hypersensitivity	Yes	3	Recovered	Related	Type IV (delayed) hypersensitivity
Ad26.Cov2.S	48/M	Hypersensitivity	No	11	Recovered	Not Related	Allergic reaction - cause unknown
Placebo	51/F	Drug hypersensitivity	No	3	Recovered	Not Related	Allergic reaction to Tylenol
Placebo	27/F	Drug hypersensitivity	No	62	Recovered	Not Related	Allergic reaction allergies - cause unknown'
Placebo	37/M	Hypersensitivity	No	5	Recovered	Not Related	Seasonal allergy (worsening)
Placebo	32/M	Hypersensitivity	No	2	Recovered	Not Related	Exacerbation of sinus allergy
Placebo	69/M	Hypersensitivity	No	17	Recovered	Not Related	Exacerbation of environmental allergy
Placebo	70/M	Hypersensitivity	No	61	Not Recovered	Not Related	Worsening of environmental allergy

Table 24: Adverse Events of Interest: Tinnitus (Study COV3001)

Study Group	Age/Sex	PT	Serious	Time to Event (Days)	Outcome	Relationship (PI)	Relevant Family / Medical History
Ad26.COV2.S	58/M	Tinnitus	No	1	Recovering	Not Related	Hypertension
Ad26.COV2.S	54/M	Tinnitus	No	17	Recovering	Not Related	Seasonal allergy
Ad26.COV2.S	63/F	Tinnitus	No	1	Recovered	Related	Hypothyroidism
Ad26.COV2.S	25/F	Tinnitus	No	2	Recovered	Related	Depression, Seasonal allergy
Ad26.COV2.S	65/F	Tinnitus	No	22	Recovering	Not Related	Migraine, Tinnitus, Vertigo
Ad26.COV2.S	51/M	Tinnitus	No	12	Not Recovered	Not Related	Hypertension, Hypothyroidism

Table 25: Adverse Events of Interest: Seizures/Convulsions (Study COV3001)

Study Group	Age/Sex	PT	Serious	Time to Event (Days)	Outcome	Relationship (PI)	Relevant Family / Medical History	Case notes
Ad26.COV2.S	41/M	Seizures	Yes	24	Recovered	Not Related	Epilepsy	Participant did not take his anti-epileptic medication the day of the event (lamotrigine 300 mg daily)
Ad26.COV2.S	25/M	Tonic-clonic seizure	No	19	Recovered	Not Related	See notes	Non-serious event reported in SAE of transverse sinus venous thrombosis / cerebral hemorrhage (secondary to the SAE)
Ad26.COV2.S	60/F	Epilepsy	No	8	Recovering	Not Related	Epilepsy, dementia	
Ad26.COV2.S	27/M	Seizures	No	29	Recovered	Not Related	-	
Placebo	53/M	Seizure	No	41	Recovered	Not Related	-	

Table 26: Adverse Events of Interest: Deep Vein Thrombosis (Study COV3001)

Study Group	Age/Sex	PT	Serious	Time to Event (Days)	Outcome	Relationship (PI)	Relevant Family / Medical History	Case notes
Ad26.COV2.S	63/M	Deep Vein Thrombosis	Yes	20	Recovered	Not related	Depression, obesity and a 'genetic mutation that made him susceptible to thrombo-embolism'	Was taken off Xarelto (Rivaroxaban) as 'he did not like taking it' 7 months prior to onset, following his retirement
Ad26.COV2.S	52/M	Deep Vein Thrombosis	No	25	Recovering	Not related	Obesity	
Ad26.COV2.S	42/M	Deep Vein Thrombosis	No	19	Not recovered	Not related		
Ad26.COV2.S	90/M	Deep Vein Thrombosis	No	13	Recovering	Not related	Chronic kidney disease, hypertension, hypothyroidism, major depression	
Ad26.COV2.S	63/M	Venous Thrombosis Limb	No	23	Recovered	Not related	Hypertension, diabetes, osteoarthritis	Event was reported as secondary to trauma
Placebo	44/M	Deep Vein Thrombosis	Yes	5	Not recovered	Related	3 paternal uncles with DVT, 4.5-hour air travel 4 days after vaccination (1 day to onset of symptoms)	
Placebo	57/M	Deep Vein Thrombosis	No	3	Not recovered	Not related	Obesity, deep vein thrombosis, hypothyroidism, oropharyngeal cancer	

Table 27: Adverse Events of Interest: Pulmonary Embolism (Study COV3001)

Study Group	Age/Sex	PT	Serious	Time to Event (Days)	Outcome	Relationship (PI)	Relevant Family / Medical History	Case notes
Ad26.COV2.S	30/F	Pulmonary Embolism	Yes	2	Recovered	Not related	Drug and alcohol abuse, contraceptive use (medroxyprogesterone)	
Ad26.COV2.S	72/M	Pulmonary Embolism	Yes	35	Not recovered	Not related	Hypertension, obesity	Positive COVID-19 case. Participant developed, while hospitalized kidney, failure and PE
Ad26.COV2.S	52/M	Pulmonary Embolism	Yes	44	Recovered	Not related	Obesity, hypertension, hereditary hemochromatosis	
Ad26.COV2.S	68/M	Pulmonary Embolism	No	20	Not recovered	Not related	COPD, hypertension, dyslipidaemia, Gout, hypothyroidism, insulin resistance, tonsillitis, urinary tract infection,	
Placebo	53/M	Pulmonary Embolism	Yes	29	Recovering	Not related	Obesity, obstructive sleep apnea, hyperlipidemia, hypertension	Positive COVID-19 test

12.5 Appendix: AdVac® Clinical Exposure and Safety Experience

Table 28: AdVac® Clinical Exposure and Safety Experience

Layer	Dataset	Cutoff	Blinding Status	Number of Participants Vaccinated with an Ad26-based Vaccine	SAEs / SUSARs (blinded or unblinded) Source: Global Safety Database	Solicited AEs, unsolicited AEs, SAEs Source: Clinical Trial Database
1	Adenoviral Vaccine Safety Database V5.0 (10 April 2020)	20 Dec 2019	✓ Unblinded	4,874	✓ Unblinded	Pooled tables including extensive sub analyses, clinical laboratory evaluation and pregnancy outcome summary
	<ul style="list-style-type: none"> Pooled data from 26 completed and ongoing¹ clinical studies Ebola, HIV, Malaria, RSV and Filovirus Ad26-based vaccine programs <p>1: For some studies, the long-term extension or follow-up period is still ongoing</p>					
2	Data from 7 ongoing and completed² unblinded³ clinical studies	21 Dec 2020	✓ Unblinded (sponsor level)	4,015	✓ Unblinded	Non-pooled safety data (study level only), including clinical laboratory evaluation
	<ul style="list-style-type: none"> Zika, HPV and RSV Ad26-based vaccine programs <p>2: Database was locked after AdVac V5.0 data cutoff 3: RSV studies unblinded at sponsor level only</p>					
3	Data from 12 Ongoing blinded studies⁴	21 Dec 2020	- Blinded	28,292	- Blinded	Blinded, non-pooled safety data (study level only), including clinical laboratory evaluation
4	Ongoing Open Label studies (Ebola)	21 Dec 2020	✓ Unblinded	20,423	✓ Unblinded	Not available
	<ul style="list-style-type: none"> Ebola vaccination campaign Democratic Republic of the Congo (DRC-EB-001 / VAC52150EBL3008), non-Janssen Sponsored study 					
5	Ongoing Open Label vaccination campaign (Ebola)	21 Dec 2020	✓ Unblinded	133,019	✓ Unblinded	Not available
6	Non-Janssen sponsored studies using Janssen's Ad26-based vaccines (Ebola)	21 Dec 2020	✓ Unblinded and blinded	3,208	✓ Unblinded and blinded	Limited safety data available (study level only)
Total Ad26 Exposure		21 Dec 2020	-	193,831	-	-

- 1 For some studies, the long-term extension or follow-up period is still ongoing.
- 2 Database was locked after AdVac V5.0 data cut-off
- 3 RSV studies unblinded at sponsor level only
- 4 Number is approximate, based on study randomization ratio