Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation

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

COVID-19 Vaccine Ad26.COV2.S

VAC31518 (JNJ-78436735)

JANSSEN'S BRIEFING MATERIALS

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

MEETING DATE: 15 OCTOBER 2021

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ad26	adenovirus type 26
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLS	capillary leak syndrome
COVID-19	coronavirus disease-2019
CT	computerized tomography
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
EU	ELISA unit
EUA	Emergency Use Authorization
FAS	Full Analysis Set
Fc	crystallizable fragment
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GBS	Guillain-Barré Syndrome
GMC	geometric mean concentration
GMI	geometric mean increase
GMT	geometric mean titer
HIV	human immunodeficiency virus
IC_{50}	50% inhibitory concentration
ICU	intensive care unit
IM	intramuscular(ly)
JBDA	Janssen Bioassay Development and Automation
KM	Kaplan-Meier
LOD	limit of detection
MAAE	medically-attended adverse event
NI	non-inferiority
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PP	Per-protocol (efficacy)
PPI	Per-protocol Immunogenicity
psVNA	pseudovirus neutralization assay
PV	pharmacovigilance
RNA	ribonucleic acid
RSA	Republic of South Africa
RT-PCR	reverse-transcriptase polymerase chain reaction
RWD	real-world data
RWE	real-world effectiveness
S	spike
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV(-2)	severe acute respiratory syndrome coronavirus(-2)
SMQ	Standardised MedDRA Queries
SpO_2	oxygen saturation
TTO	time-to-onset
TTS	thrombosis with thrombocytopenia syndrome
US	United States

Abbreviation	Definition
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VNA	virus neutralization assay
VOC	variant of concern
VOI	variant of interest
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, recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike (S) protein, developed by Janssen Biotech, Inc. (Janssen). It received Emergency Use Authorization (EUA) on 27 February 2021 for the prophylactic immunization against coronavirus disease-2019 (COVID-19) in adults aged 18 years or older. Ad26.COV2.S is currently administered as a single dose intramuscular (IM) injection of 5×10^{10} viral particles (vp) in a liquid volume of 0.5 mL. On 4 October 2021, Janssen submitted a Amendment to EUA application to seek approval of a booster dose of Ad26.COV2.S administered IM in adults aged 18 years or older.

Note that in the context of clinical studies presented in this document in which immunocompetent adult participants (with and without comorbidities) received a second dose of Ad26.COV2.S ($5x10^{10}$ vp), the terms "booster" and "Dose 2" are used interchangeably, as all participants had shown a response (both in enzyme-linked immunosorbent assay [ELISA] and functional antibodies) after the first dose, and all showed a rapid rise of antibodies within a week after administration of the second dose, the second dose is effectively a boost.

A single dose of Ad26.COV2.S elicited a durable humoral and cellular immune responses up to at least 6 to 8 months post vaccination and durable protection against **severe/critical COVID-19**[1] (including hospitalizations and deaths related to COVID-19) up to at least 6 months post vaccination in adults ≥18 years of age. In COV3001, no waning of protection against moderate to severe/critical COVID-19 was observed in the United States (US) over the observation period. However, a decrease in protection over time against **moderate to severe/critical COVID-19** globally was observed which was driven by reduced efficacy against some of the emerging SARS-CoV-2 variants in regions outside the US. A single dose of Ad26.COV2S elicited a neutralizing antibody response against SARS-CoV-2 variants of concern (VOCs) but the response was lower compared to the reference strain.

Based on recent data, administration of a booster dose resulted in increased protection against symptomatic COVID-19, increased strength and breadth of immune responses against variants and increase protection against severe/critical COVID-19.

Early interim analysis results of a large Janssen real world data (RWD) cohort study (study COV4002) confirmed that the vaccine efficacy (VE) observed in the pivotal study COV3001 translates into clinical practice, with sustained effectiveness (VE against observed COVID-19 and COVID-19 related hospitalization) measured as of 14 days after vaccination to a maximum of 183 days after vaccination. Ad26.COV2.S vaccine effectiveness for COVID-19 and hospitalizations

[1] Note that COVID-19 severity case definitions are provided in Appendix 2. In study context, the term 'symptomatic COVID-19' is used to indicate mild, moderate and severe/critical COVID-19 according to these definitions. The primary case definition of moderate to severe/critical COVID-19 was so comprehensive that a very few cases were found to be outside of this definition and considered mild. Therefore, the terms moderate to severe/critical COVID-19 and symptomatic COVID-19 are used interchangeably.

was consistently effective and stable month-over-month, including when the Delta variant emerged to when it became dominant in June-August 2021.

To address the non-inferiority (NI) of a booster dose of Ad26.COV2.S versus a primary regimen, Janssen designed an adequately powered Phase 2 study COV2008 to evaluate the immunogenicity, reactogenicity and safety of Ad26.COV2.S administered as booster vaccination in adults ≥18 years of age ≥6 months after receiving a primary vaccination with Ad26.COV2.S (in study COV3001) or Pfizer's BNT162b2 (2-dose). The study is currently ongoing and no data are yet available, except for preliminary dose level-blinded reactogenicity data. A post-hoc NI analysis was performed on 17 participants from COV1001 who received a booster dose 6 months after the first dose. While the study did not include a pre-specified non-inferiority objective, the fold increase in the ELISA assay and the psuedovirus neutralization assay (psVNA) from 28 days post dose 1 to 7 days post booster dose (Day 190) and from 28 days post dose 1 to 28 days post booster dose (Day 211) have met the standard NI criteria.

However, in this document the sponsor presents evidence that a homologous booster dose of Ad26.COV2.S after the initial dose substantially increases efficacy and immunogenicity:

An Ad26.COV2.S booster dose administered 2 months after the primary Ad26.COV2.S dose substantially increases protection, especially against symptomatic COVID-19, including when caused by SARS-CoV-2 variants of concern (see table below) . The primary analysis results of Janssen's 2-dose efficacy study COV3009 includes data from 7484 participants who received 2 doses of Ad26.COV2.S and 7008 participants who received 2 doses of placebo in the PP set. Median follow-up time after the second dose in the double-blind phase was 36 days (0-172 days), with 29.3% of participants in the per protocol set with at least 2 months of follow-up after the 2nd dose. Sequencing data were available from 68.0% of cases in the double-blind phase of the study. The reference sequence was only present in 6.0% of the sequenced strains overall and 22.9% in the US.

In the US, where the dominant strain during the double-blind phase of COV3001 (single dose regimen) was the reference strain, VE was stable when comparing the COV3001 primary and final analysis. After the Ad26.COV2.S booster dose (COV3009), VE against symptomatic COVID-19 was 94% in the US.

	COV3009 primary analysis, VE 14 days after Ad26.COV2.S booster dose	**COV3001 final analysis double-blind phase, VE 28 days after single Ad26.COV2.S dose**
Symptomatic COVID-19*		
US	94% (95% CI 59;100)	70% (95% CI 61;77)
Global	75% (95% CI 55;87)	53% (95% CI 47,58)
Severe/Critical COVID-19		
Global	100% (adjusted 95% CI 33 100.00)	75% (adjusted 95% CI 65;82)

* moderate to severe/critical COVID-19 per the case definitions in Appendix 2.

The number of cases in COV3009 that were infected with the Alpha or Mu variant were sufficient to allow a variant specific analysis of vaccine efficacy, which demonstrated that a homologous booster of Ad26.COV2.S increases protection against symptomatic infection for different variants. At the analysis cut-off date in June 2021, the Delta variant was not yet prominent in our study population, so vaccine efficacy for this variant are not available.

Studies COV1001 and COV2001 indicate that a larger interval between the primary vaccination with Ad26.COV2.S and a homologous booster dose results in a larger increase in humoral immune responses (ELISA titers) versus the 1-dose regimen, for both participants 18-55 years of age and ≥65 years of age, going from a 4-6 fold increase (both age groups) with a 2-month boost to a 12-fold increase with a 6-month boost (younger age group only). Therefore, vaccine efficacy against symptomatic infection may increase further.

A total of 9,379 participants ≥18 years of age, including 2,383 participants ≥60 years of age, have received 2 doses of Ad26.COV2.S 5×10^{10} vp in clinical studies, with the booster administered after an interval of 2 months to ≥6 months. Overall, Ad26.COV2.S has an acceptable reactogenicity profile after both the first dose and booster, with the reactogenicity post-booster being similar or milder than post-dose 1. No new safety concerns have been identified after an Ad26.COV2.S booster.

In conclusion, the efficacy and safety data presented in this briefing document support a favorable benefit-risk profile for Ad26.COV2.S when given as a booster dose after the single dose primary regimen in adults ≥18 years of age.

Based on the recent data, it can be assumed that the administration of the booster dose will result in increased protection against symptomatic infection, increased strength and breadth of immune responses against current variants, and increase of the magnitude of protection against severe disease across populations. The booster dose can also increase the probability of protection against future variants of concern.

A booster dose is recommended at 6 months or later, based on the strength of the immune responses, although a booster dose may be administered as early as 2 months. The need for a booster dose and/or its timing will depend on the local/epidemiological situation and the needs of individuals/specific populations.

In the early stages of a pandemic, a single dose vaccine is an efficient tool to rapidly increase vaccine uptake and reduce the burden on health care systems by preventing severe disease outcomes, especially where supply limitations were present. In the current stage of the pandemic, and given emergence of different variants under certain circumstances, focus may shift to protecting individuals by maximizing and prolonging vaccine-induced protection, not only against severe/critical COVID-19, but also against symptomatic infection, to potentially reduce transmission, and raise immunity to increase the probability of protection against future variants of concern. This is important in the US, where the low vaccination coverage puts even vaccinated

people at risk because of strong circulation of the highly transmissible delta variant. A booster dose of the Janssen COVID-19 vaccine was shown to safely increase protection against all forms of COVID-19 and should therefore be considered for optimal individual protection.

2. BACKGROUND INFORMATION AND RATIONALE FOR AN AD26.COV2.S BOOSTER DOSE

The availability of highly effective vaccines against COVID-19 has ensured significant progress in the fight against COVID-19 and vaccination remains the most effective method for a long-term strategy for prevention and control of COVID-19 in the foreseeable future. Over 14 million US citizens received the Janssen COVID vaccine, Ad26.COV2.S as a single dose primary regimen. The single-shot Janssen COVID-19 vaccine has consistently demonstrated strong (74.6%) protection against severe/critical COVID-19 and death without evidence of waning protection (see Section 2.1). However, the occurrence of variants seems to impact VE against symptomatic COVID-19. The administration of a booster dose will strengthen immune responses and ensure optimal and durable protection against symptomatic COVID-19 as well as increase protection against severe/critical COVID-19 across populations and SARS-CoV-2 variants (see Section 2.2). The administration also aligns with the priority in the US to optimally protect individuals to any SARS-CoV-2 infection. Therefore, Janssen is requesting EUA for the administration of a homologous booster for recipients of single-dose Janssen COVID-19 vaccine. Data supporting the indication is provided in Section 3.

2.1. Background Information

2.1.1. Ad26.COV2.S Single Dose Primary Regimen – Pivotal Phase 3 Study COV3001

The EUA was mainly supported by the primary analysis of the pivotal Phase 3 study COV3001 (ENSEMBLE; see Appendix 1 for the study design). The primary analysis of the COV3001, performed when the 2-month median follow-up timepoint was reached (database cut-off date: 22 January 2021), demonstrated that a single dose of Ad26.COV2.S is effective against symptomatic COVID-19 and highly effective in the prevention of severe/critical COVID-19, particularly in prevention of hospitalization and death. Note that COVID-19 severity case definitions are provided in Appendix 2. In study context, the term ‘symptomatic COVID-19’ is used to indicate mild, moderate and severe/critical COVID-19 according to these definitions. The primary case definition of moderate to severe/critical COVID-19 was so comprehensive that a very few cases were found to be outside of this definition and considered mild. Therefore, the terms moderate to severe/critical COVID-19 and symptomatic COVID-19 are used interchangeably. At the time of the primary analysis, predominant SARS-CoV-2 strains were the reference strain in the US (Wuhan B.1 D614G), Beta VOC in the Republic of South Africa (RSA), and the Zeta variant (P.2) in Brazil.

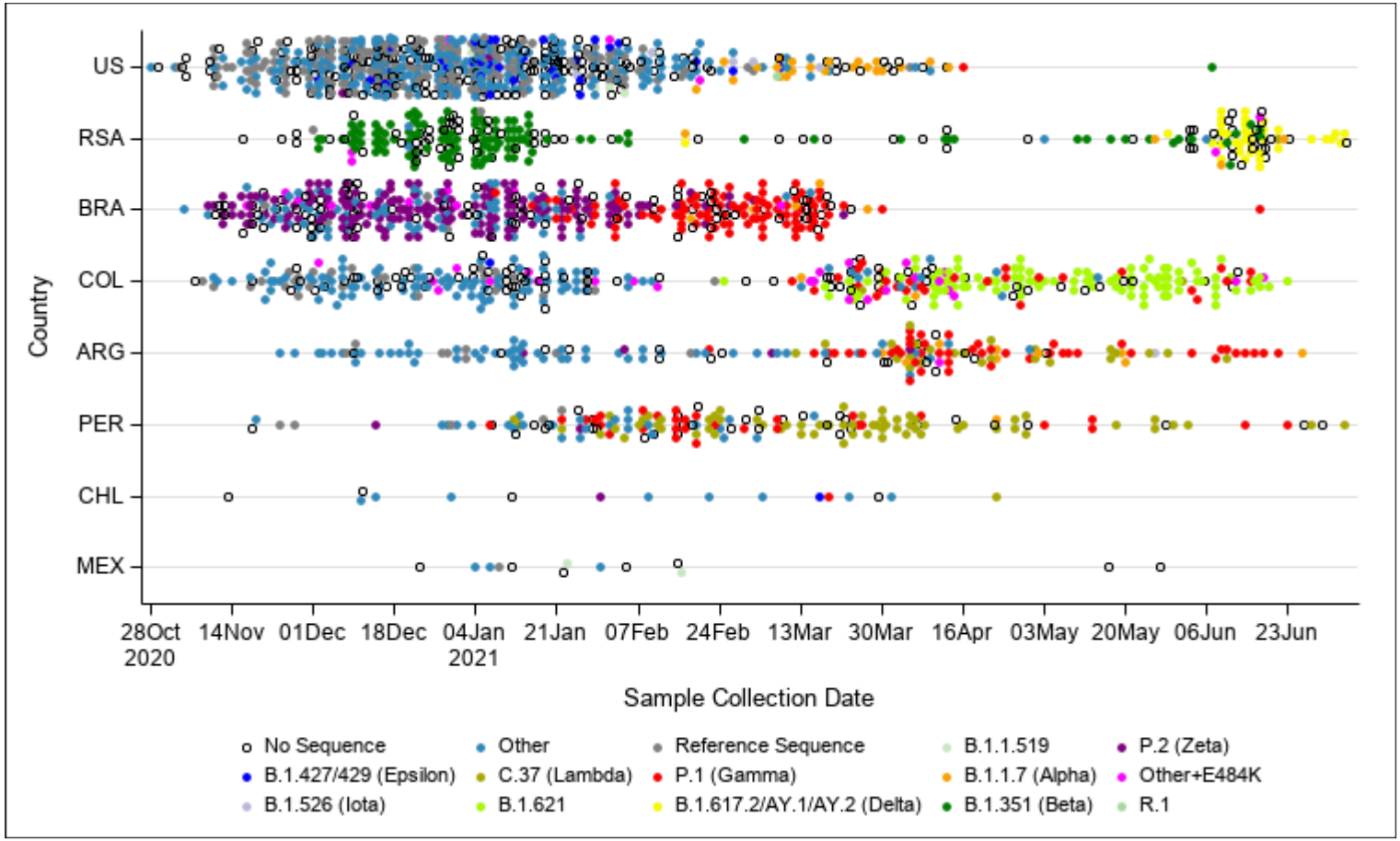
Following EUA, the study protocol was amended to allow participants to become unblinded at which time the participants who received placebo were offered the Ad26.COV2.S vaccine. As the study amendment was implemented at different calendar times depending on the country, this

resulted in regional differences in duration of the double-blind follow-up at the time of the final analysis (cut-off date: 9 July 2021).

At the time of the final analysis of the double-blind phase, the median follow-up time was 4 months and 22.8% of participants in the per protocol set had at least 6 months (defined as 24 weeks) of double-blind follow-up.

During the study, the incidence of SARS-CoV-2 infection was highly variable in time and between regions (Figure 1). The dominant strains at the time of the primary analysis (cut-off date 22 January 2021; 2 months median follow-up) were replaced by new variants during the subsequent follow-up period. As of 12 February 2021, at the time of the primary analysis, sequencing data were available from 512 out of 714 cases (71.7%) which showed that the reference strain was present in 63.7 % (94.4% in US) while in the remaining cases with sequence data available, Beta (16.8%), variants with E484K mutation (other than 20H/501Y.V2 [Beta lineage] and 20J/501Y.V3 [Gamma lineage]; 18.6%) and CAL.20C (epsilon; 1.0 %) were detected. At the time of the final analysis, as of 9 July 2021, sequencing data were available for 1,589 out of the 2,056 cases (77.3%) in the double-blind phase of the study (full analysis set as of Day 1). At the final analysis, the reference sequence was only present in 14.0% of the sequenced strains overall and 37.4% in the US (Table 1) while the Alpha variant was present in 2.7% of the sequenced strains overall and 4.7% in the US. In the US, the Alpha VOC emerged after March 2021. Also, in most other countries where the study was being conducted new lineages of the virus emerged and became dominant. In the RSA, the Delta VOC was observed during the time of unblinding/cross-over (June 2021). Within the study population, the Zeta variant in Brazil was replaced by the Gamma VOC, which also emerged in Peru, Argentina, and Colombia, at various moments in time following the primary analysis. In Peru, at the same time the Lambda VOI emerged, while in Colombia, the Mu variant of interest (VOI) was observed simultaneously. Other variants (including variants with E484K mutation) were also observed (Figure 1). An overview of the case accrual by variant is provided overall and for the US specifically in (Table 1).

Figure 1: Occurrence Over Time of SARS-CoV-2 Variants for All Subjects, Including Cases Not Sequenced; Full Analysis Set (Study VAC31518COV3001)



Cut-off date for the primary analysis: 22 January 2021; cut-off date of the final analysis: 9 July 2021
Last available visit date across countries 1-9 July, Last available onset primary endpoint: June 9 (Arg), Mar 24 (Bra), Apr 22 (Chl), June 23 (COL), 15 Feb (Mex), Jul 1 (Peru), Apr 16 (US), July 5 (South Africa)
Reference sequence is defined as the SARS-CoV-2 Wuhan-Hu1 Sequence with the addition of amino acid variation D614G
Sequencing was performed using NGS Swift assay using 1% and baseline polymorphisms defined with a cut-off of 15%.
Amino acid variations are defined as changes from the reference sequence.
Considered Substitution Profiles:
B.1.1.7 (Alpha): H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,S982A,T716I,D1118H
B.1.351 (Beta): K417N,E484K,N501Y,D614G, A701V
P.1 (Gamma): K417T,E484K,N501Y,D614G,H655Y
B.1.617.2/AY.1/AY.2 (Delta): L452R,T478K,D614G,P681R
B.1.427/429 (Epsilon): W152C,L452R,D614G
B.1.525 (Eta): A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L
B.1.526 (Iota): L5F,T95I,D253G,D614G,E484K, A701V
B.1.617.1 (Kappa): G142D,E154K,L452R,E484Q,D614G,P681R
C.37 (Lambda): R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N
P.3 (Theta): L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F
P.2 (Zeta): E484K,D614G,V1176F (not part of P.1 or P.3)
B.1.621 (Mu): T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N
C.36.3: W152R,R346S,L452R,D614G,Q677H,A899S
R.1: W152L,E484K,D614G,G769V
B.1.1.519: T478K, D614G,P681H,T732A
Other+E484K: only E484K and no other variant; Other: Any sequences with mutations not leading to another variant

[GVICE_COV01A1.RTF] [VAC31518\VAC31518COV3001\DBR_IA_FINAL_DB\RE_IA_FINAL_DB\PROD\GVICE_COV01BA12.SAS] 31AUG2021, 03:48

Table 1: Proportion of Molecularly Confirmed Cases Infected with SARS-CoV-2 Variant with S Protein Amino Acid Variation Versus the SARS-CoV-2 Reference Sequence with Substitution Profile for Blinded Subjects*, Full Analysis Set (Study VAC31518COV3001)

total number of cases	2056
subjects with sequencing data	1589 (77.3%)
Reference Sequence	223 (14.0%)
Variant Sequence	
B.1.1.7 (Alpha)	43 (2.7%)
B.1.351 (Beta)	124 (7.8%)
B.1.617.2/AY.1/AY.2 (Delta)	36 (2.3%)
B.1.427/429 (Epsilon)	35 (2.2%)
B.1.525 (Eta)	0
P.1 (Gamma)	203 (12.8%)
B.1.526 (Iota)	6 (0.4%)
B.1.617.1 (Kappa)	0
C.37 (Lambda)	94 (5.9%)
P.3 (Theta)	0
P.2 (Zeta)	180 (11.3%)
B.1.621 (Mu)	103 (6.5%)
C.36.3	0
R.1	1 (0.1%)
B.1.1.519	6 (0.4%)
Other+E484K	43 (2.7%)
Other	492 (31.0%)
United States total number of cases	621
United States subjects with sequencing data	470 (75.7%)
Reference Sequence	176 (37.4%)
Variant Sequence	
B.1.1.7 (Alpha)	22 (4.7%)
B.1.351 (Beta)	1 (0.2%)
B.1.617.2/AY.1/AY.2 (Delta)	0
B.1.427/429 (Epsilon)	33 (7.0%)
B.1.525 (Eta)	0
P.1 (Gamma)	1 (0.2%)
B.1.526 (Iota)	5 (1.1%)
B.1.617.1 (Kappa)	0
C.37 (Lambda)	0
P.3 (Theta)	0
P.2 (Zeta)	2 (0.4%)
B.1.621 (Mu)	0
C.36.3	0
R.1	1 (0.2%)
B.1.1.519	4 (0.9%)
Other+E484K	3 (0.6%)
Other	222 (47.2%)

Table 1: Proportion of Molecularly Confirmed Cases Infected with SARS-CoV-2 Variant with S Protein Amino Acid Variation Versus the SARS-CoV-2 Reference Sequence with Substitution Profile for Blinded Subjects*, Full Analysis Set (Study VAC31518COV3001)

* All cases and sequence data obtained during the double-blinded study phase.
Note: The denominator is the number of cases with sequencing data available at the case episode.
Reference sequence is defined as the SARS-CoV-2 Wuhan-Hu1 Sequence with the addition of amino acid variation D614G
Amino acid variations are defined as changes from the reference sequence. Sequencing was performed using NGS Swift assay using 1% and baseline polymorphisms defined with a cut-off of 15%.
Considered Substitution Profiles:
B.1.1.7 (Alpha): H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,S982A,T716I,D1118H
B.1.351 (Beta): K417N,E484K,N501Y,D614G, A701V
P.1 (Gamma): K417T,E484K,N501Y,D614G,H655Y
B.1.617.2/AY.1/AY.2 (Delta): L452R,T478K,D614G,P681R
B.1.427/429 (Epsilon): W152C,L452R,D614G
B.1.525 (Eta): A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L
B.1.526 (Iota): L5F,T95I,D253G,D614G,E484K, A701V
B.1.617.1 (Kappa): G142D,E154K,L452R,E484Q,D614G,P681R
C.37 (Lambda): R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N
P.3 (Theta): L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F
P.2 (Zeta): E484K,D614G,V1176F (not part of P.1 or P.3)
B.1.621 (Mu): T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N
C.36.3: W152R,R346S,L452R,D614G,Q677H,A899S
R.1: W152L,E484K,D614G,G769V
B.1.1.519: T478K, D614G,P681H,T732A
Other+E484K: only E484K and no other variant; Other: Any sequences with mutations not leading to another variant

2.1.1.1. Ad26.COV2.S Single Dose Primary Regimen – Efficacy Study COV3001

Based on the final efficacy analysis of the double-blind phase of the pivotal Phase 3 study COV3001, the study continues to meet its co-primary objectives: VE (95% confidence interval [CI]) against molecularly confirmed moderate to severe/critical COVID-19 was 56.3% (51.30; 60.84) when considering cases from at least 14 days after vaccination and 52.9% (47.06; 58.08) when considering cases from at least 28 days after vaccination. Vaccine efficacy against symptomatic COVID-19 is similar as for the primary objective given the limited number of mild cases.

Vaccine efficacy remained highest against severe/critical COVID-19 with a VE (95% CI) of 73.3% (63.94; 80.49) when evaluated at least 14 days after vaccination and 74.6% (64.70; 82.06) when evaluated at least 28 days after vaccination, including VE in the prevention of medical intervention and deaths. All COVID-19-related deaths occurring in the Ad26.COV2.S group were at the time of the primary analysis and in older adults with comorbidities.

Table 2: Vaccine Efficacy – Final Analysis COV3001

	14 days post vaccination		28 days post vaccination	
	VE	95% CI*	VE	95% CI*
Moderate and severe/critical COVID-19	56.3%	(51.30; 60.84)	52.9%	(47.06; 58.08)
All SARS-CoV-2 infections	-	-	41.7%	(36.32; 46.71)*
Symptomatic COVID-19 severity	55.9%	(50.95; 60.46)	52.4%	(46.63; 57.64)
Mild	29.4%	(-64.57; 70.66)	19.9%	(-102.28; 69.00)
Moderate	52.1%	(46.11; 57.40)	47.2%	(40.21; 53.51)
Severe/ critical	73.3%	(63.94; 80.49)	74.6%	(64.70; 82.06)
Req. Medical intervention	76.1%	(56.86; 87.67)*	75.6%	(54.26; 88.00)*
COVID-19 related deaths[a]	84.5%	(47.30; 97.06)	82.8%	(40.49; 96.77)
Asymptomatic SARS-CoV-2 infections	-	-	28.9%	(19.99;36.78)*

Analysis set: per protocol: 19,577 and 19,608 participants in the Ad26.COV2.S and placebo group, respectively;
risk set at 14 days post vaccination: 19,400 and 19,398 participants in the Ad26.COV2.S and placebo group, respectively
risk set at 28 days post vaccination: 19,113 and 18,924 participants in the Ad26.COV2.S and placebo group, respectively
The risk set are all subjects of the Per Protocol Set excluding subjects that had a positive PCR test between day 1 and day 14 or day 28, respectively
* The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.
[a].A fatality is COVID-19 related if it is COVID-related according to the adjudication committee or it has a fatal adverse event that is COVID-19 related after the onset of a COVID-19 episode with at least 1 documented PCR

Vaccine efficacy, against severe/critical COVID-19 was generally consistent across age groups, participants without/with comorbidities, regions, countries and against SARS-CoV-2 variants with sufficient cases, including the Beta, Gamma VOCs and Lambda, Mu VOIs.

Analyses by SARS-CoV-2 strains demonstrated an estimated VE (95% CI) against molecularly confirmed moderate to severe/critical COVID-19 with the reference strain and pooled variant strains (excluding the reference strain) of 71.5% (57.31; 81.39) and 43.6% (34.19; 51.67), respectively, when evaluated at least 14 days after vaccination. VE estimates against molecularly confirmed moderate to severe/critical COVID-19 with the reference strain and pooled variant strains (excluding the reference strain) were 58.2% (34.96; 73.72) and 44.1% (34.35; 52.56), respectively, when evaluated at least 28 days after vaccination. When considering the different SARS-CoV-2 variants, including VOCs/VOIs, emerging at different stages throughout the study and in different countries, variations in the level of protection against moderate to severe/critical COVID-19 was observed. The wide CIs for certain VE estimates should be considered when concluding on the level of protection. There was no reduction in VE estimates compared to that of the reference strain (VE estimate [95%CI] 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants, while the VE (95% CI) estimates for the Delta (5.7% [-177.7; 59.23]) and Gamma (35.6% [12.99; 52.61]) VOCs, Mu (35.9% [1.69; 58.65]) and Lambda (10.1% [-39.23; 42.11%]) VOIs were reduced. The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). For the Delta VOC there were a limited number of COVID-19 cases (21 moderate to severe/critical cases: 11 in the Ad26.COV2.S group versus 10 in the placebo group, of which 2 cases in each group were severe/critical), and these appeared late (>5.5 months after vaccination) in the study. The limited data and wide CIs do not allow drawing relevant conclusions on vaccine efficacy against this VOC.

Vaccine efficacy (95% CI) against molecularly confirmed severe/critical COVID-19 with the reference strain and pooled variant strains of 89.7% (57.33; 98.84) and 70.0% (54.72; 80.61), respectively, when evaluated at least 14 days after vaccination and 93.1% (54.39; 99.84) and 71.8% (56.31; 82.34), respectively, when evaluated at least 28 days after vaccination. VE estimates against severe/critical COVID-19 were generally 63%-91% across variants with sufficient COVID-19 cases, such as Beta and Gamma VOCs and Lambda and MU VOIs. For the Alpha VOC (2 versus 4 moderate to severe/critical cases in the Ad26.COV2.S group versus the placebo group) and the Delta VOC (2 in each group), no conclusions can be drawn given the limited number. Wide CIs for certain VE estimates should be considered when interpreting the data.

In the US, where the dominant strain during the double-blind phase was the reference strain, VE against moderate to severe/critical COVID-19 was 72.9% (65.74;78.70) and 69.7% (60.72;76.90) at least 14 days and 28 days post vaccination, respectively and VE against severe/critical COVID-19 was 69.0% (37.31;85.82) and 74.4% (39.49;90.63), respectively. This is similar to what was observed during the primary analysis (VE against moderate to severe/critical COVID-19: 76.6% [65.45;84.63] and 72.2% [53.12;84.22], respectively and VE against severe/critical COVID-19: 71.7% [9.81;93.21] and 1 vs 4 cases, respectively). Only limited data are available for the Delta variant. Overall, there were 9 moderate cases in the Ad26.COV2.S group versus 8 moderate cases in the placebo group, all of which occurred 5.5-7.5 months post vaccination and 2 severe cases in both the Ad26.COV2.S and placebo group. However, real world data (RWD) from a large cohort study conducted in the US, including at the time the Delta variant became highly prevalent, are available and provide more comprehensive information on this variant. Data are described in Section 2.1.3.

2.1.1.2. Ad26.COV2.S Single Dose Primary Regimen – Onset and Duration of Protection

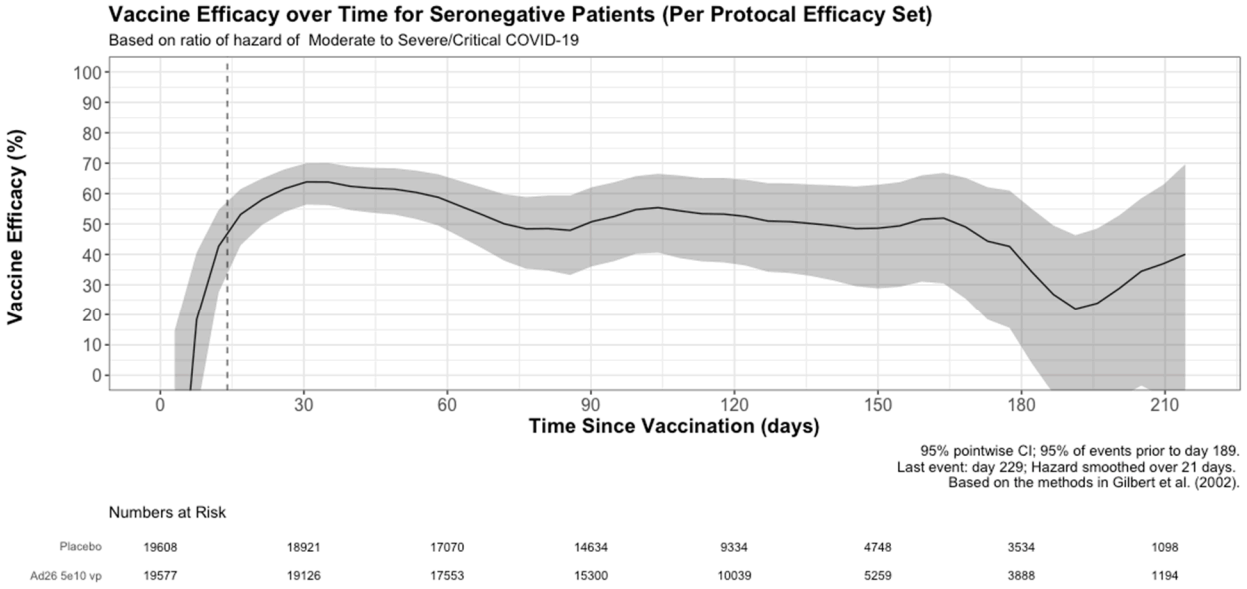
Based on Kaplan-Meier (KM) curves, the onset of efficacy against **moderate to severe/critical COVID-19** was evident as of 14 days after a single Ad26.COV2.S dose. Vaccine efficacy increased in the first weeks after vaccination and reduced afterwards (see Figure 2 and Table 3). No waning of protection against moderate to severe/critical COVID-19 was observed in the US over the observation period (Figure 3).

The onset of protection against **severe/critical COVID-19** starts around 7 days after vaccination, increases over time up to around 45 days, and remains stable afterwards (around 70%) up to 6 months post vaccination, with the emergence of certain SARS-CoV-2 variants, including VOCs/VOIs (see Figure 4).

Several of the variants were observed between 2 to 6 months after vaccination. When focusing on variants with an overlapping timeframe of observation (reference strain, Alpha VOC, Gamma VOC, Lambda VOI, and other mutations), the VE was relatively stable over time. This suggests that the reduced VE against moderate to severe/critical COVID-19 since the primary analysis (see Table 4) is likely driven by reduced VE against some variants (such as Gamma VOC, and Lambda and Mu VOIs) (see Figure 5). For other variants, insufficient data were available to make conclusions.

In summary, although protection against severe/critical COVID-19, COVID-19 related hospitalization and COVID-19 related death is sustained up to at least 6 months after vaccination with a single dose of Ad26.COV2.S, protection against moderate to severe/critical COVID-19 was shown to decline over time, indicating that actually the protection against moderate COVID-19 declines over time, which could be driven by reduced VE against SARS-CoV-2 variants.

Figure 2: Vaccine Efficacy Over Time of Molecularly Confirmed Moderate to Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination, PP Set (Seronegative; Study VAC31518COV3001) Final Analysis of Double-Blind Phase



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

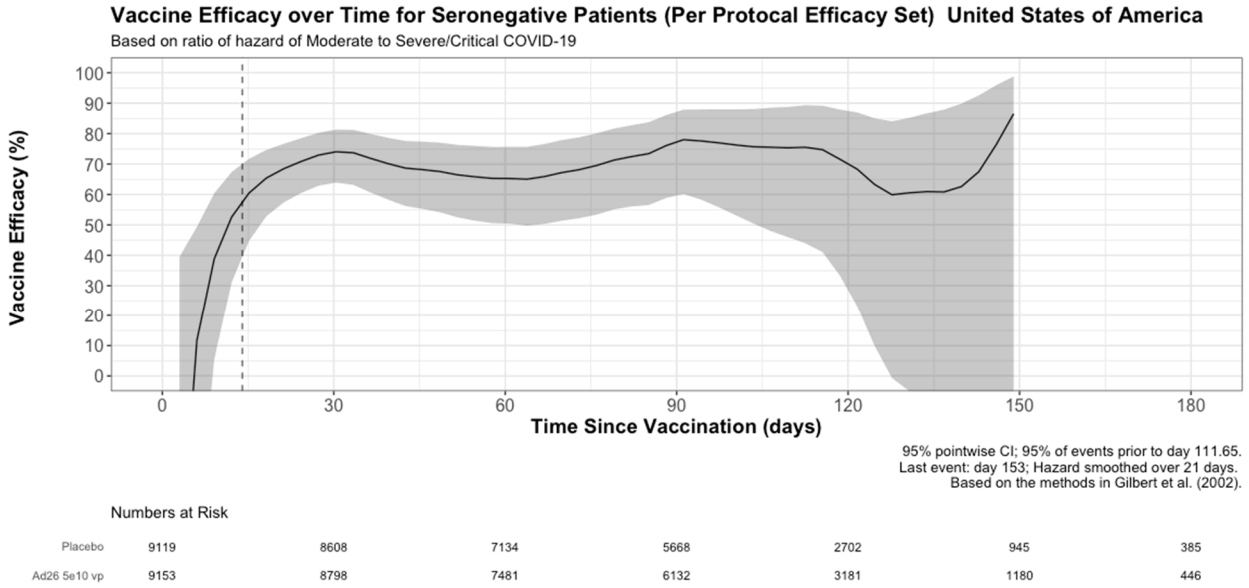
Table 3: Vaccine Efficacy of Molecularly Confirmed Moderate to Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination; Per Protocol Set Final Analysis of Double-Blind Phase Study (VAC31518COV3001)

	Ad26 5e10 vp		Placebo		
	#Cases (N)	PY	#Cases (N)	PY	VE% (95% CI)
Analysis set: PP	(19577)		(19608)		
Moderate to severe/critical[a]					
Day 2 to Day 14	82 (19577)	748.66	88 (19608)	749.83	6.7% (-27.54; 31.77)
Day 15 to Day 28	51 (19400)	1483.44	184 (19398)	1480.09	72.3% (62.10; 80.13)
Day 29 to Day 56	119 (19113)	2877.42	306 (18924)	2837.44	61.7% (52.46; 69.23)
Day 57 to end DB Phase	314 (17586)	6460.98	573 (17090)	6158.91	47.8% (39.95; 54.62)
Day 57 to Day 112	157 (17586)	5040.02	308 (17090)	4860.10	50.8% (40.24; 59.70)
Day 113 to end DB Phase	157 (11379)	4900.35	265 (10572)	4529.34	45.2% (33.04; 55.34)

PY: Person Years; VE: Vaccine Efficacy; CI: Confidence Interval; PP: Per Protocol Set; NE: Not Evaluable.
[a]First molecularly confirmed moderate to severe/critical COVID-19 case

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

Figure 3: Vaccine Efficacy Over Time of Molecularly Confirmed Moderate to Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination - US, PP Set (Seronegative; Study VAC31518COV3001) Final Analysis of Double-Blind Phase



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

Table 4: Vaccine Efficacy Against Moderate to Severe/critical COVID-19 With Onset at Least Days After Vaccination: Primary Analysis Versus Final Analysis, Per Protocol Set (Study VAC31518COV3001)

Country	Post-dose	Analysis* and Day	Moderate to Severe COVID-19 Ad26.COV2.S vs Placebo	Vaccine Efficacy (95%CI)
All	3001: Post-dose 1	Primary Analysis: Day > 28		**66.1%** (55.0, 74.8)
		Final Analysis: Day > 28		**52.9%** (47.1, 58.1)
United States	3001: Post-dose 1	Primary Analysis: Day > 28		**72.0%** (58.2, 81.7)
		Final Analysis: Day > 28		**69.7%** (60.7, 76.9)

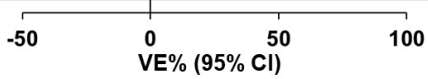
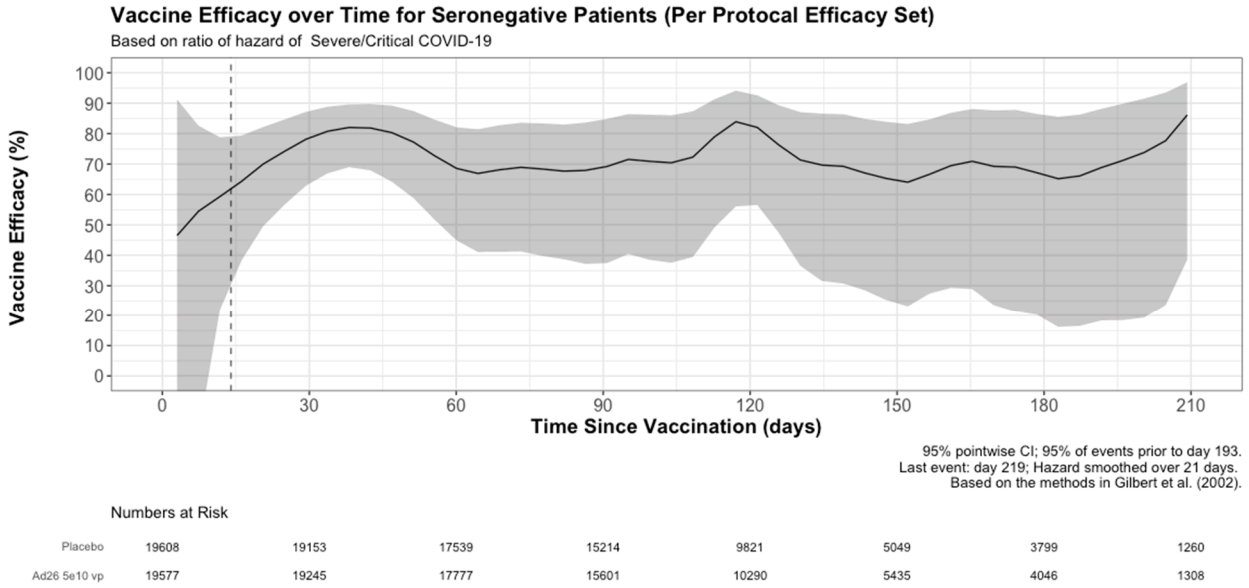


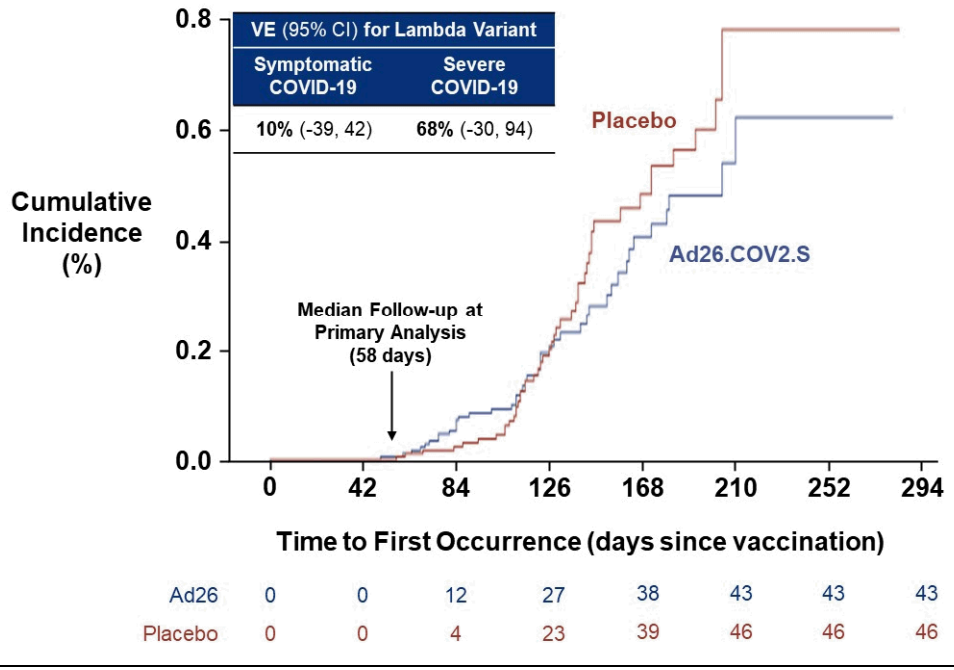
Figure 4: Vaccine Efficacy Over Time of Molecularly Confirmed Severe/Critical COVID-19 with Onset at Least 1 Day After Vaccination, PP Set (Seronegative; Study VAC31518COV3001) Final Analysis of Double-Blind Phase



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

Figure 5: VE Against Symptomatic Infection* for Lambda (C.37), Gamma (P.1) and Mu (B.1.621) Variant (COV3001)

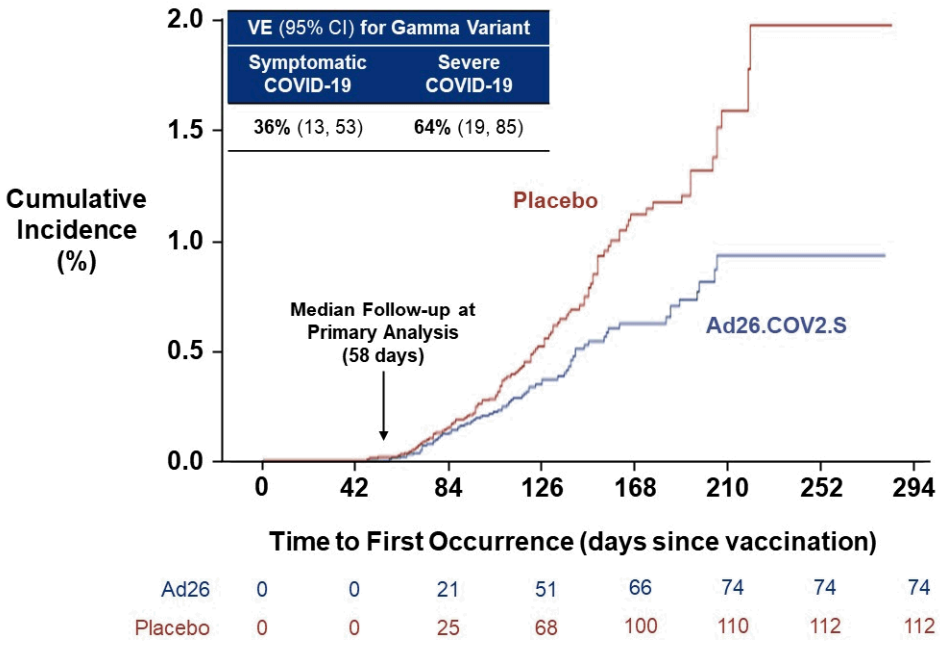
Lambda (C37) Variant



Vaccine Efficacy Over Time for Lambda against Symptomatic COVID-19

Time Period (Days)	Cases		VE (95% CI)
	Ad26	PBO	
2 to 14	0	0	--
15 to 28	0	0	--
29 to 70	5	3	**-67%** (-973, 68)
71 to 112	13	11	**-18%** (-191, 51)
113 to 154	16	23	**30%** (-38, 66)
155 to 196	7	6	**-17%** (-320, 66)
197 to 238	2	3	--

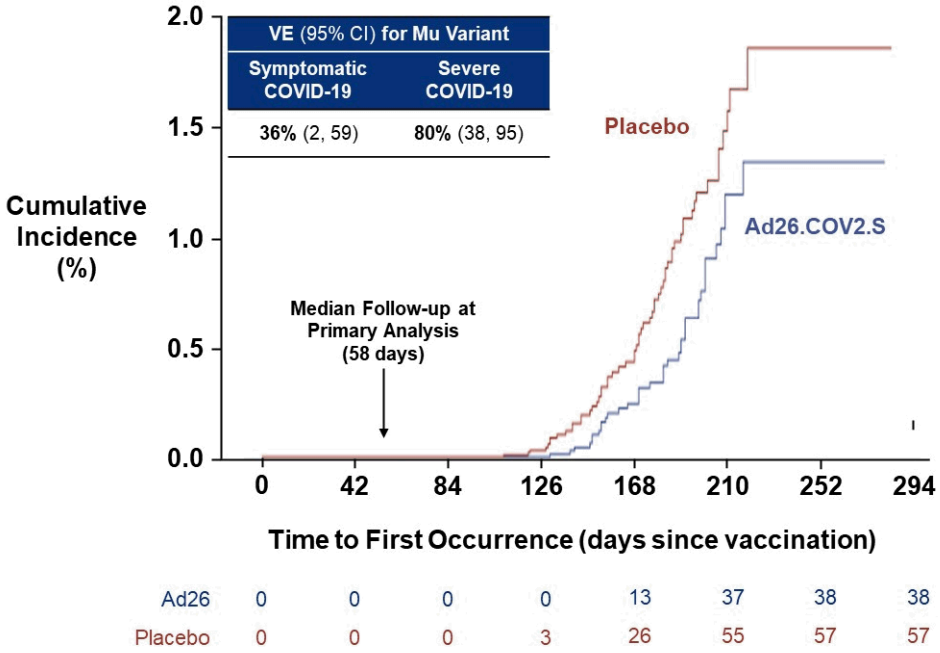
Gamma (P.1) Variant



Vaccine Efficacy Over Time for Gamma against Symptomatic COVID-19

Time Period (Days)	Cases		VE (95% CI)
	Ad26	PBO	
2 to 14	0	0	--
15 to 28	0	0	--
29 to 70	6	12	**50%** (-44, 85)
71 to 112	36	44	**18%** (-30, 49)
113 to 154	21	37	**43%** (0, 68)
155 to 196	8	13	**39%** (-60, 78)
197 to 238	3	6	**50%** (-134, 92)

Mu (B.1.621) Variant



Vaccine Efficacy Over Time for Mu against Symptomatic COVID-19

Time Period (Days)	Cases		VE (95% CI)
	Ad26	PBO	
2 to 14	0	0	--
15 to 28	0	0	--
29 to 70	0	0	--
71 to 112	0	1	--
113 to 154	9	18	**50%** (-17, 80)
155 to 196	18	31	**42%** (-7, 69)
197 to 238	11	7	**-57%** (-378, 44)

* Moderate to severe/critical COVID-19 per the case definitions in Appendix 2

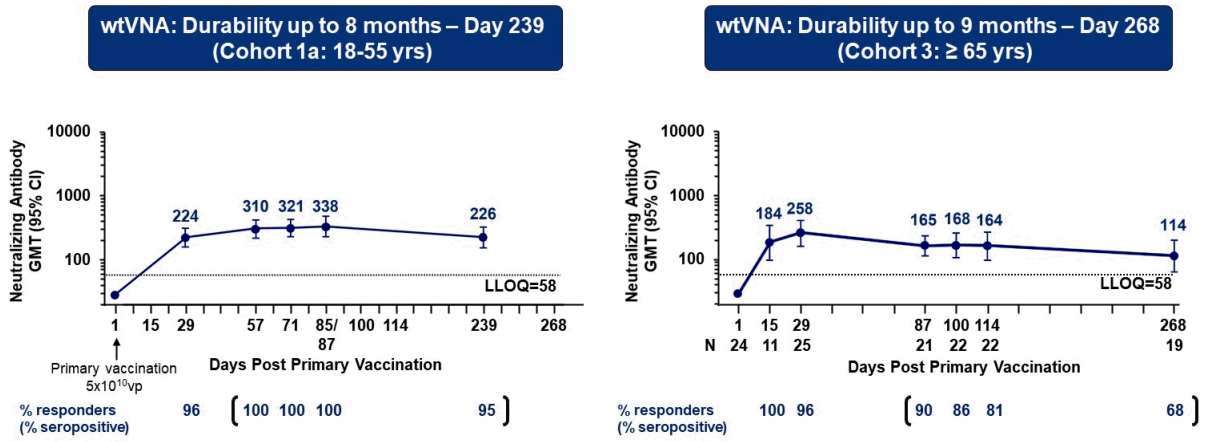
2.1.1.3. Ad26.COV2.S Single Dose Primary Regimen – Safety

An overview of the safety and reactogenicity of the single-dose Ad26.COV2.S regimen is provided in Section 4.1

2.1.2. Ad26.COV2.S Single Dose Primary Regimen – Durability of Immune Response

Data on the durability of humoral responses against the original SARS-CoV-2 strain up to 8 months (Day 239) after 1 dose of Ad26.COV2.S ($5x10^{10}$ vp) are available from Phase 1 study COV1001. The data showed that SARS-CoV-2 neutralizing antibodies increase over time up to approximately 3 months post primary vaccination and remain stable for up to at least 8 months after vaccination in participants 18-55 of age. In participants ≥65 years of age, a decline in responses is observed between 6 and 8 months after vaccination (see Figure 6). Note that a high level of correlation between S protein binding antibodies versus neutralizing antibodies has been observed (see Section 3.6).

Figure 6: Humoral Immune Responses Over Time Following a Single Dose of Ad26.COV2.S (StudyCOV1001)



Neutralizing antibodies against SARS-CoV-2 variants of concern, ie, Alpha (B.1.1.7, VUI2020 12/01, Kent), Beta (B.1.351, 20H/501Y.V2, RSA) and Delta (B.1.617.2) after 1 dose of Ad26.COV2.S at the of 5×10^{10} vp level, were measured in selected samples from participants aged 18-55 of age in COV1001. A single dose of Ad26.COV2.S is shown also to be immunogenic against SARS-CoV-2 VOCs. However, immune sera from obtained 28 days after a single dose of Ad26.COV2.S showed lower neutralizing activity against the Alpha, Beta and Delta variants, respectively, compared to the original strain. At Day 71 the neutralizing activity against all 3 variants had increased, and the difference in neutralizing activity against the original strain and variant strains had reduced. Specifically for the Delta variant, neutralization at Day 29 was more than 37-fold lower than neutralization of the original strain. The 50% inhibitory concentration (IC_{50}) titers increased between Day 29 and Day 71 in 4/6 participants tested, giving a geometric mean titer (GMT) which was approximately 14-fold lower compared to the original strain, a

smaller difference than observed at Day 29. At Day 239, 8 months after a single dose of 5×10^{10} vp Ad26.COV2.S, responses showed a slight decline. The GMT against the Delta variant was lower than Day 71 levels but slightly higher than the response at Day 29.

The durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination was recently also described in Barouch 2021. Barouch 2021 reports on the antibody and T-cell responses on Day 239 (8 months after the single-shot [10 participants] or 6 months after the 2-shot vaccine regimen of Ad26.COV2.S [10 participants]) as well as neutralizing antibody responses against the parental WA1/2020 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and against the SARS-CoV-2 variants D614G, B.1.1.7 (alpha), B.1.617.1 (kappa), B.1.617.2 (delta), P.1 (gamma), B.1.429 (epsilon), and B.1.351 (beta). These data show that the Ad26.COV2.S vaccine elicited durable humoral and cellular immune responses with minimal decreases for at least 8 months after immunization. In addition, an expansion of neutralizing antibody breadth against SARS-CoV-2 variants over this time period was observed, including against the more transmissible B.1.617.2 variant and the partially neutralization-resistant B.1.351 and P.1 variants, which suggests maturation of B-cell responses even without further boosting.

2.1.3. Ad26.COV2.S Single Dose Primary Regimen – RWD Cohort Study

Janssen in collaboration with Health Verity, Aetion and Harvard, conducted a large, observational, longitudinal US RWD (study COV4002) cohort study to assess effectiveness (VE against observed COVID-19 and COVID-19 related hospitalization) of the Ad26.COV2.S vaccine using de-identified multimodal RWD with national coverage (HealthVerity data). HealthVerity COVID-19 data consists of de-identified patient-level RWD for ~160M patient lives submitted by US providers of inpatient, outpatient, pharmacy and laboratory services from March 1 2020, through August 31 2021.

Study eligible individuals ≥18 years of age who received a single dose of Ad26.COV2.S between March 1, 2021 and August 17, 2021 were eligible to enter the study cohort on the day of vaccination. Individuals with evidence of prior COVID-19 signs, symptoms, infection or, receipt of any COVID-19 vaccine during the 365 days before cohort entry were excluded. The follow-up period started 14 days after date of vaccination until the earliest of the occurrence of an outcome, receipt of any COVID-19 vaccine, loss to follow-up, or August 31, 2021 (includes months of dominant delta variant- July and August 2021).

To achieve balance between the Ad26.COV2.-vaccinated and unvaccinated cohorts, the cohorts were direct matched by age (± 4 years), sex, location (3-digit ZIP), time, and comorbidities. In addition, cohorts were further propensity score matched on predictors for COVID-19 severity. The two outcomes assessed were

1. observed COVID-19 defined as a diagnosis of an in- or outpatient ICD-10-CM diagnosis code of U07.1 in any position, and/or a recorded positive or presumptive positive SARS-CoV-2 diagnostic nucleic acid amplification polymerase chain reaction (PCR) test result, and

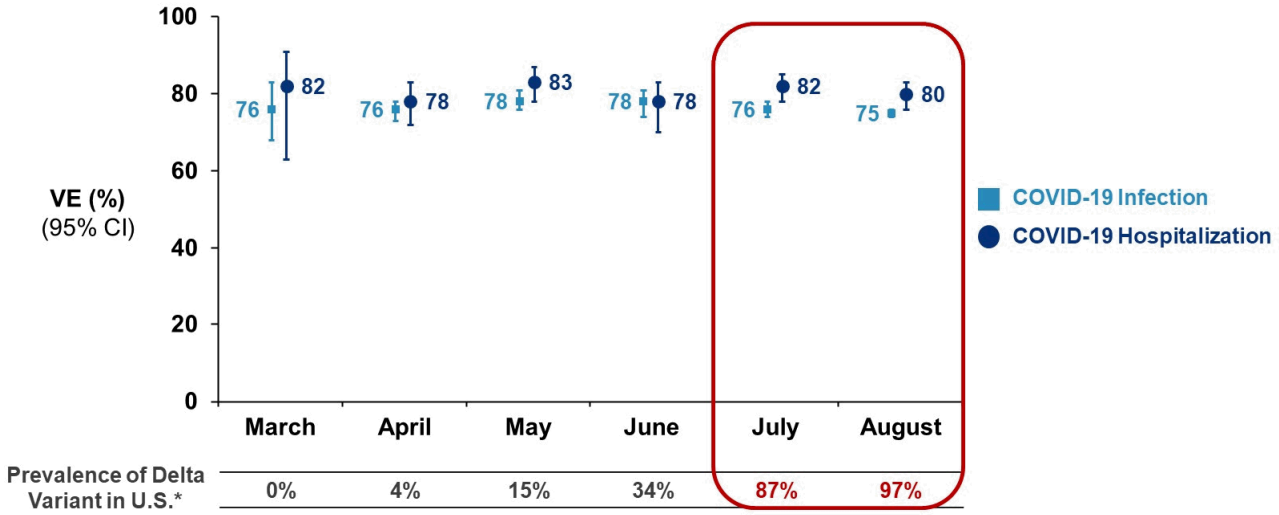
2. COVID-19-related hospitalization defined as any claim for an inpatient stay with a discharge diagnosis of COVID-19 or a recorded infection (defined previously) within 21 days before admission.

A correction factor was applied to all estimates of vaccine effectiveness to account for under-recording of vaccination status in healthcare claims. A sizeable proportion of individuals who received a vaccination at mass vaccination sites, employers, pharmacies and other settings may not have an insurance claim in the HealthVerity data source as there was no fee associated with the vaccine. Therefore, a substantial proportion of the unvaccinated group in the data source may in fact be vaccinated, thus observed vaccine effectiveness estimates will appear lower than the true vaccine effectiveness. Based on calculations made by considering vaccination rates in the US reported by the Centers for Disease Control and Prevention (CDC) in July 2021 (57% of US residents or 162M vaccinated of 283M), and the vaccinations seen in the HealthVerity data at that time (34% or 54M vaccinated of 161M), a 40% under-recording of vaccinations was assumed for the analyses and a correction factor was applied to all vaccine effectiveness estimates. In sensitivity analyses, we varied the under-recording assumption from 0% to 70% in 10% increments. Subsequent results showed that that uncorrected vaccine effectiveness is ~10 percentage points lower than corrected vaccine effectiveness.

Early interim analysis results of this RWD study confirmed that the VE observed in the pivotal study COV3001 translates into clinical practice, with sustained effectiveness starting 14 days after vaccination to a maximum of 183 days after vaccination with the median follow-up of 129 days for observed COVID-19 and 130 days for COVID-19 related hospitalization (Appendix 5). Ad26.COV2.S vaccine effectiveness for COVID-19 and hospitalizations was consistently effective and stable month-over-month, including when the Delta variant emerged to when it became dominant in June-August 2021 (Figure 7). Examining the incidence of observed COVID-19 and COVID-19-related hospitalization as a function of time since vaccination, a stable vaccine effectiveness starting 14 days after vaccination to a maximum of 183 days after vaccination was observed (Figure 8). Visual inspection of Schoenfeld residual plots for any observed COVID-19 and COVID-19 related hospitalization indicated that the hazard ratio was generally constant over time and that there was no observed VE reduction during follow-up (Figure 9). Subgroup analyses showed that vaccine effectiveness for immunocompromised individuals, individuals with Type 2 Diabetes Mellitus and individuals ≥65 years have lower vaccine effectiveness than the overall cohort (Appendix 5). In addition, month-over-month analyses and tine to event analyses up to 183 days after vaccination in the 65+ years subgroup demonstrate that the vaccine effectiveness is stable and long-lasting over calendar time (Figure 11).

The vaccine effectiveness results in Janssen's large, longitudinal US cohort study demonstrated effective and stable vaccine effectiveness for the single-dose Ad26.COV2S vaccine based on month-over-month analysis and KM plots through the end of August 2021. There have been several other RWE studies that have been recently published by researchers, that evaluate the vaccine effectiveness of single dose Ad26.COV2.S vaccine. A summary table of these published RWE studies is provided in Appendix 3. Several factors should be considered that may influence measures of VE and limit direct study comparisons between these studies, including different study designs and outcome definitions and systematic differences in study populations such as underlying comorbidities and other risk factors, as well as demographics including socioeconomic factors. Additionally methodological considerations such as appropriate matching of comparator cohorts, time since vaccination, follow-up times, and several other bias considerations make it difficult to directly compare point estimates for vaccine effectiveness across studies. Despite these limitations, it is important to note that results from several studies (Bekker 2021, Corchado-Garcia 2021, Moline 2021, de Gier 2021) align with the Janssen study showing effective VE of the single-dose Ad26.COV2.S vaccine, with one study (de Gier 2021) also showing that the VE does not wane with time since vaccination up to 20 weeks after full vaccination.

Figure 7: Month-Over-Month Vaccine Effectiveness (March 2021 – August 2021) - RWD



* Nextstrain 2021

Figure 8: COVID-19-related Outcomes by Time Since Vaccination+14 Days

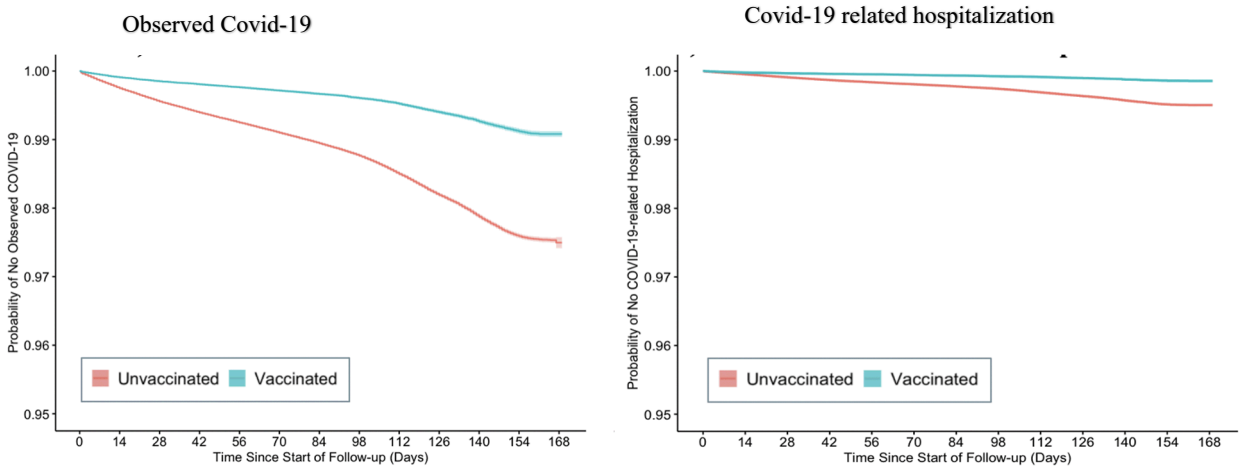


Figure 9: Plot of Schoenfeld Residuals for Primary Analysis

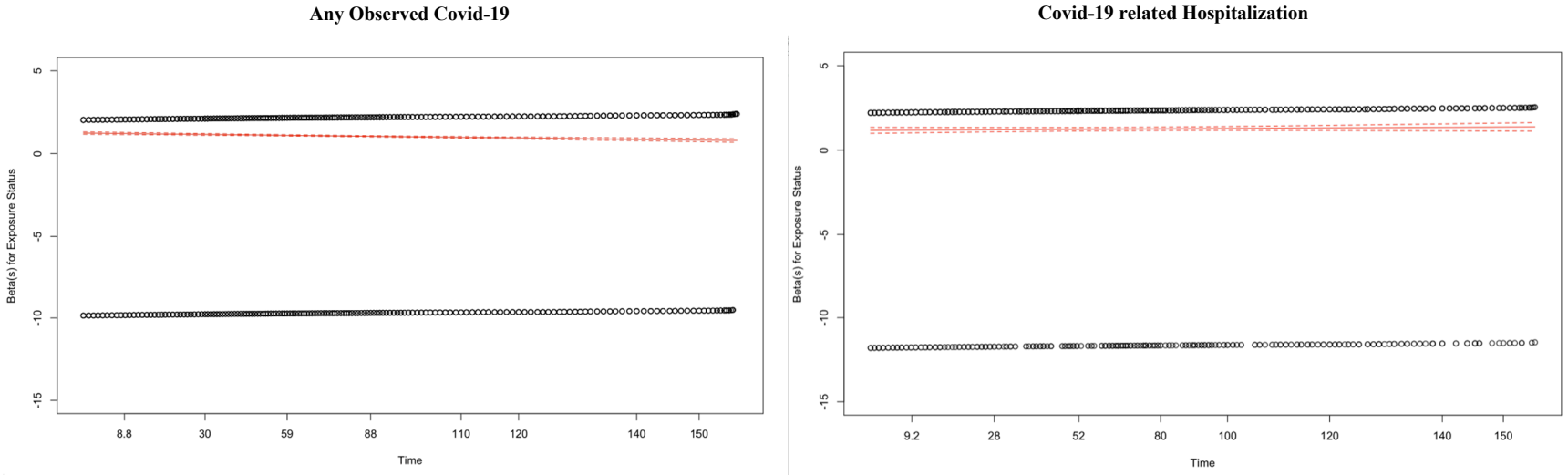


Figure 10: Month-Over-Month Vaccine Effectiveness in 65+ Age Group (March 2021 – August 2021)

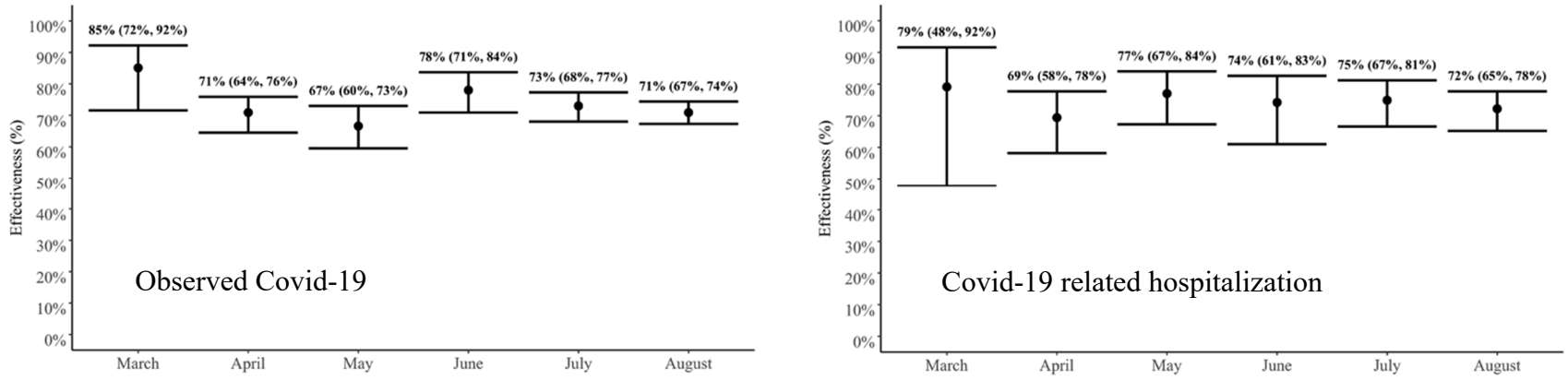
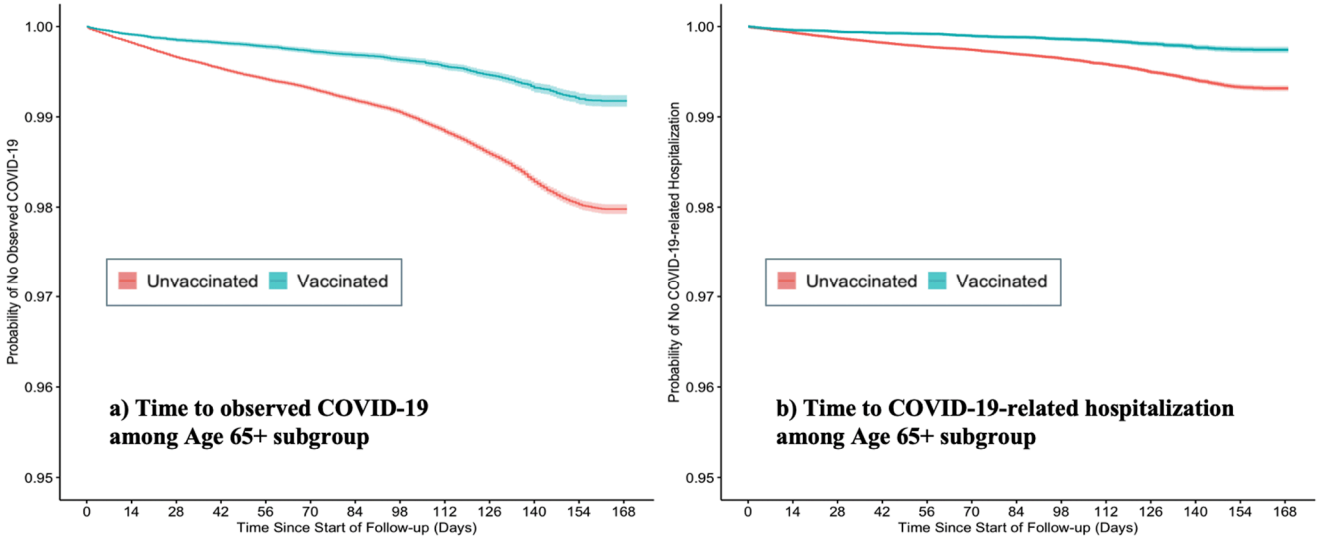


Figure 11: COVID-19 Related Outcomes by Time Since Vaccination (+14 days) in Age 65+ Age Group



Follow-up day 0 is equivalent to 14 days post-index, as follow-up for outcomes begins 14 days after vaccination or matched index date. Kaplan-Meier plots include 95% confidence intervals around the survival function.

2.2. Rationale for an Ad26.COV2.S Booster Dose

The availability of highly effective vaccines against COVID-19 has ensured significant progress in the fight against COVID-19 and vaccination remains the most effective method for a long-term strategy for prevention and control of COVID-19 in the foreseeable future. However, long-term follow-up of vaccine study participants has revealed a growing risk of breakthrough infections. Also for other vaccines a decrease in protection has been observed. The emergence of new variants of SARS-CoV-2 that confer an increase in transmissibility, more severe disease (increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination and reduced effectiveness of treatments and/or vaccines is currently of concern. This raises the possibility that current COVID-19 vaccine regimens may provide reduced protection against these variants. Hence, it is important now to focus on further protecting individuals maximizing and prolonging vaccine-induced protection, not only against severe/critical COVID-19, but also against symptomatic infection, to potentially reduce transmission, and raise immunity to increase the probability of protection against future variants of concern.

Booster vaccinations, in general, have been proven to strengthen or maintain immune responses and to ensure long lasting protection following vaccination. It has been suggested that a booster shot of COVID-19 vaccine will be needed to maximize and prolong vaccine-induced protection, also against variants.

A single dose of Ad26.COV2.S elicited a durable humoral and cellular immune responses up to at least 6 to 8 months post vaccination and durable protection against **severe/critical COVID-19** (including hospitalizations and deaths related to COVID-19) up to at least 6 months post vaccination in adults ≥18 years of age. In COV3001, no waning of protection against moderate to severe/critical COVID-19 was observed in the US over the observation period. However, a decrease in protection over time against **moderate to severe/critical COVID-19** globally was observed which was driven by reduced efficacy against some of the emerging SARS-CoV-2 variants in regions outside the US. A single dose of Ad26.COV2S elicited a neutralizing antibody response against SARS-CoV-2 VOC but the response was lower compared to the reference strain.

Based on recent data (COV3009, COV2001, COV1001), it can be assumed that the administration of a booster dose will result in increased protection against symptomatic COVID-19, increased strength and breadth of immune responses against current and future variants and increase the magnitude of protection against severe/critical COVID-19 across populations, without compromising the acceptable safety profile.

The supporting evidence is discussed in Section 3 below and based on those data, Janssen is seeking authorization for a booster dose with the following indication: *A booster dose is recommended at 6 months or later, based on the strength of the immune responses, although a booster dose may be administered as early as 2 months. The need for a booster dose and/or its*

timing will depend on the local/epidemiological situation and the needs of individuals/specific populations.

To address the NI of a booster dose of Ad26.COV2.S versus a primary regimen Janssen designed an adequately powered Phase 2 study (COV2008) that will evaluate the immunogenicity, reactogenicity and safety of Ad26.COV2.S administered as booster vaccination in adults ≥18 years of age ≥6 months after receiving a primary vaccination with Ad26.COV2.S (in study COV3001) or Pfizer's BNT162b2 (2-dose). The study is currently ongoing and no data are yet available, except for preliminary dose level-blinded reactogenicity data which are described in Section 4.2.3.2.

3. SUMMARY OF AD26.COV2.S BOOSTER DATA

The final analysis of COV3001 (see Section 2.1.1) demonstrate that the single dose Ad26.COV2.S primary regimen provides substantial protection against severe COVID-19 disease, hospitalization and death and maintains a favorable benefit-risk profile. Durable protection against observed COVID-19 and COVID-19 related hospitalizations was confirmed by large real-world-effectiveness studies in the US and South Africa, including in calendar time that the Delta variant was highly prevalent (see Section 2.1.3). Therefore, the single dose Ad26.COV2.S regimen continues to be an important tool in the fight against COVID-19.

To address the non-inferiority (NI) of a booster dose of Ad26.COV2.S versus a primary regimen, Janssen designed an adequately powered Phase 2 study COV2008 to evaluate the immunogenicity, reactogenicity and safety of Ad26.COV2.S administered as booster vaccination in adults ≥18 years of age ≥6 months after receiving a primary vaccination with Ad26.COV2.S (in study COV3001) or Pfizer's BNT162b2 (2-dose). The study is currently ongoing and no data are yet available, except for preliminary dose level-blinded reactogenicity data. A post-hoc NI analysis was performed on 17 participants from COV1001 who received a booster dose 6 months after the first dose. While the study did not include a pre-specified non-inferiority objective, the fold increase in the ELISA assay and the psVNA assay from 28 days post dose 1 to 7 days post booster dose (Day 190) and from 28 days post dose 1 to 28 days post booster dose (Day 211) have met the standard NI criteria.

In addition, the following sections demonstrate that an Ad26.COV2.S booster will further enhance protection and will maintain a favorable benefit-risk profile:

- Study COV3009 indicates that an Ad26.COV2.S booster dose 2 months after the initial dose substantially increases efficacy, especially against symptomatic infections, including when caused by SARS-CoV-2 variants of concern (see Section 3.1). In the U.S. the boosted population has a vaccine efficacy of 94%, whereas the single dose vaccine efficacy is 73%.
- Consistent with the efficacy results, immunogenicity data indicate that a booster dose 2 months after the initial dose substantially increases humoral immune responses (ELISA titers) by about 4-fold (see Section 3.2)

- Administration of an Ad26.COV2.S booster dose 6 months after the initial dose further increases humoral immune responses, increasing Ab titers by about 9-12 fold relative to day 29 levels. Therefore, vaccine efficacy against symptomatic infection may increase further (see Section 3.3).

- The Ad26.COV2.S vaccine when given as a booster had an acceptable safety profile with no new safety signals (Studies COV1001, COV2001 and COV3009) (see Section 4.2).

In addition, the following data are provided as supportive information: immunogenicity results of 2-dose vaccination with Ad26.COV2.S ($5x10^{10}$ vp) against variants of concern (Section 3.4), results on the impact of neutralizing antibodies against the Ad26 vector (Section 3.5) on Ad26.COV2.S immunogenicity, and results on the correlation between neutralizing, binding, and functional antibody responses (Section 3.6).

3.1. Efficacy in COV3009 – Booster at 2 Months

The primary objective of the global, randomized, placebo-controlled study COV3009 (ENSEMBLE 2) was to demonstrate efficacy of 2 doses of Ad26.COV2.S administered with a 56-day interval. In the study 31,300 participants were randomized to receive 2 doses of Ad26.COV2.S or placebo. The study was conducted in multiple regions (North and South America, Africa, Europe and Asia) at a time when new lineages of the virus were emerging (see Figure 12). Efficacy data described below are from the final analysis (end-of double-blind phase).

As during the study, participants could be unblinded as soon as eligible for another authorized/approved vaccine and after the EUA of Ad26.COV2.S each participant was unblinded and those who originally received placebo were offered Ad26.COV2.S. Therefore, the fraction of participants who received 2 doses of Ad26.COV2S during the double-blind phase was limited (53.5%) as was the median follow-up after the second dose in the double-blind phase (36 days [range: 0-172 days]). The number of participants in the per protocol set with at least 2 months of follow-up post vaccination was 4,245 (29.3%). As a result, the number of COVID-19 cases available for evaluation of the second dose is limited and, therefore, data within subgroups should be interpreted with caution.

During the study, the incidence of SARS-CoV-2 infection was highly variable in time and between regions. New lineages of the virus emerged and became dominant in most of the countries where the study was being conducted. At the time of the final analysis, sequencing data were available from 319 out of the 469 cases (68.0%) in the double-blind phase of the study. The reference sequence was only present in 6.0% of the sequenced strains overall and 22.9% in the US (Table 5).

Figure 12: Occurrence Over Time of SARS-CoV-2 Variants for Blinded Subjects, Including Cases Not Sequenced; Full Analysis Set (Study VAC31518COV3009)

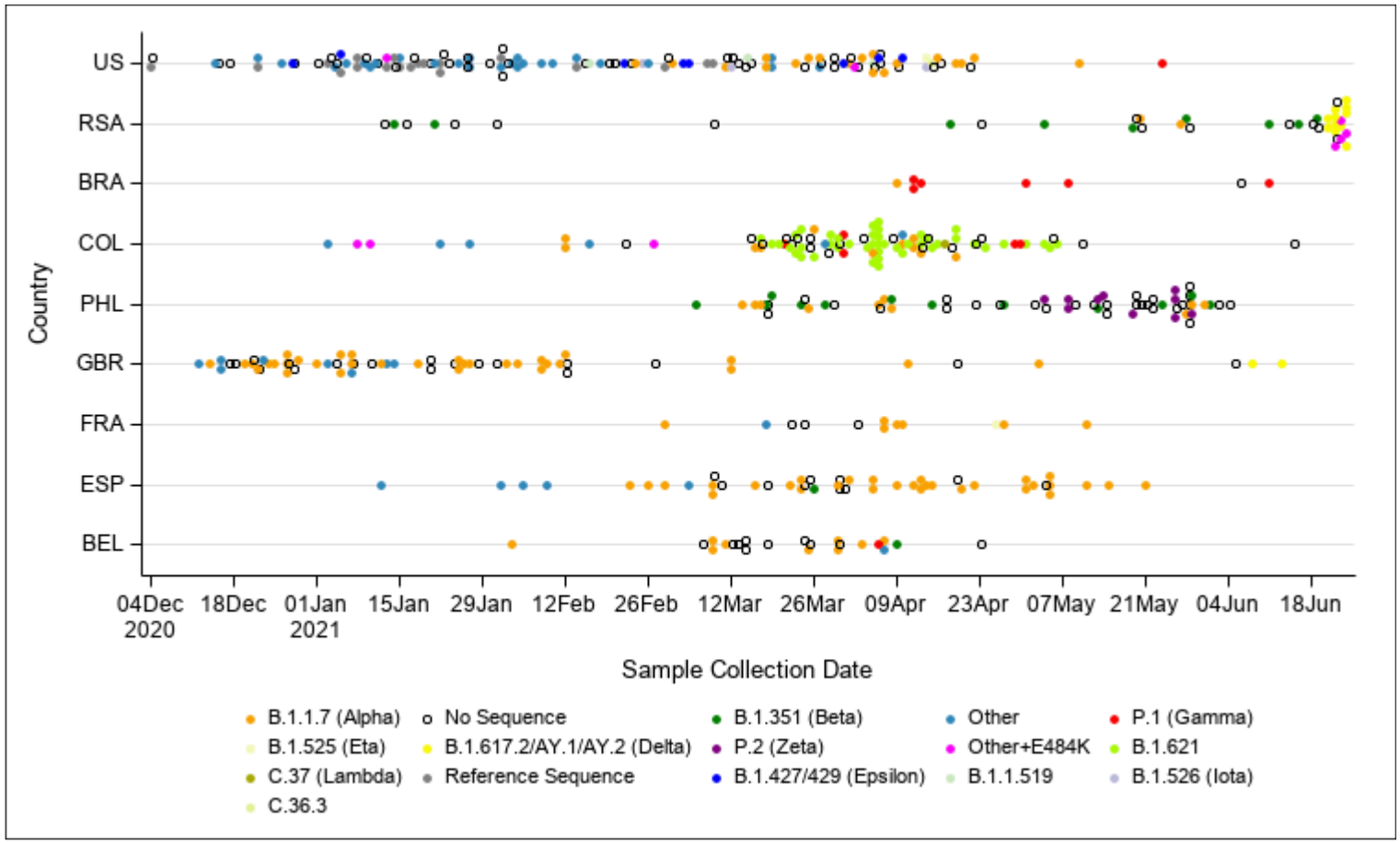


Figure 12: Occurrence Over Time of SARS-CoV-2 Variants for Blinded Subjects, Including Cases Not Sequenced; Full Analysis Set (Study VAC31518COV3009)

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

Case accrual by variants where sequence data were available.
FAS analysis set (N=31,300); cases: 468; cases with sequencing data: 319
VOC: variant of concern (only 1 variant designated as VOC (CDC.gov 2021)

[GVICE_COV01A1.RTF] [VAC31518\VAC31518COV3009\DBR_IA1\RE_IA1\PROD\GVICE_COV01BA12.SAS] 27AUG2021, 18:55

Table 5: Proportion of Molecularly Confirmed Cases Infected with SARS-CoV-2 Variant with S Protein Amino Acid Variation Versus the SARS-CoV-2 Reference Sequence with Substitution Profile for Blinded Subjects*, Full Analysis Set (Study VAC31518COV3009)

total number of cases	469
subjects with sequencing data	319 (68.0%)
Reference Sequence	19 (6.0%)
Variant Sequence	
B.1.1.7 (Alpha)	122 (38.2%)
B.1.351 (Beta)	23 (7.2%)
B.1.617.2/AY.1/AY.2 (Delta)	13 (4.1%)
B.1.427/429 (Epsilon)	8 (2.5%)
B.1.525 (Eta)	2 (0.6%)
P.1 (Gamma)	13 (4.1%)
B.1.526 (Iota)	3 (0.9%)
B.1.617.1 (Kappa)	0
C.37 (Lambda)	1 (0.3%)
P.3 (Theta)	0
P.2 (Zeta)	10 (3.1%)
B.1.621 (Mu)	45 (14.1%)
C.36.3	1 (0.3%)
R.1	0
B.1.1.519	3 (0.9%)
Other+E484K	9 (2.8%)
Other	47 (14.7%)
United States total number of cases	127
United States subjects with sequencing data	83 (65.4%)
Reference Sequence	19 (22.9%)
Variant Sequence	
B.1.1.7 (Alpha)	19 (22.9%)
B.1.351 (Beta)	0
B.1.617.2/AY.1/AY.2 (Delta)	0
B.1.427/429 (Epsilon)	8 (9.6%)
B.1.525 (Eta)	1 (1.2%)
P.1 (Gamma)	1 (1.2%)
B.1.526 (Iota)	3 (3.6%)
B.1.617.1 (Kappa)	0
C.37 (Lambda)	0
P.3 (Theta)	0
P.2 (Zeta)	0
B.1.621 (Mu)	0
C.36.3	1 (1.2%)
R.1	0
B.1.1.519	3 (3.6%)
Other+E484K	2 (2.4%)
Other	26 (31.3%)

* All cases and sequence data obtained during the double-blinded study phase.
Note: The denominator is the number of cases with sequencing data available at the case episode.
Reference sequence is defined as the SARS-CoV-2 Wuhan-Hu1 Sequence with the addition of amino acid variation D614G
Amino acid variations are defined as changes from the reference sequence. Sequencing was performed using NGS Swift assay using 1% and baseline polymorphisms defined with a cut-off of 15%.
Considered Substitution Profiles:
B.1.1.7 (Alpha): H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,S982A,T716I,D1118H
B.1.351 (Beta): K417N,E484K,N501Y,D614G, A701V
P.1 (Gamma): K417T,E484K,N501Y,D614G,H655Y
B.1.617.2/AY.1/AY.2 (Delta): L452R,T478K,D614G,P681R

Table 5:	**Proportion of Molecularly Confirmed Cases Infected with SARS-CoV-2 Variant with S Protein Amino Acid Variation Versus the SARS-CoV-2 Reference Sequence with Substitution Profile for Blinded Subjects*, Full Analysis Set (Study VAC31518COV3009)**
total number of cases	469
B.1.427/429 (Epsilon): W152C,L452R,D614G	
B.1.525 (Eta): A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L	
B.1.526 (Iota): L5F,T95I,D253G,D614G,E484K, A701V	
B.1.617.1 (Kappa): G142D,E154K,L452R,E484Q,D614G,P681R	
C.37 (Lambda): R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N	
P.3 (Theta): L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F	
P.2 (Zeta): E484K,D614G,V1176F (not part of P.1 or P.3)	
B.1.621 (Mu): T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N	
C.36.3: W152R,R346S,L452R,D614G,Q677H,A899S	
R.1: W152L,E484K,D614G,G769V	
B.1.1.519: T478K, D614G,P681H,T732A	
Other: Any sequences with mutations not leading to another variant	

As of at least 14 days after the second vaccination, the 2-dose regimen was efficacious in the prevention of moderate to severe/critical COVID-19 (primary endpoint) with a VE of 75.2% (14 versus 52 cases, adjusted 95% CI [54.55;87.30]) and in the prevention of severe/critical COVID-19 with a VE of 100% (0 versus 8 cases, adjusted 95% CI: [32.62; 100.00]) (Table 6).

Data show that VE at least 14 days after the first dose of Ad26.COV2.S (VE [95% CI] against moderately to severe/critical COVID-19 and severe critical COVID-19: 67.9% [57.95;75.79] and 92.4% [75.92;98.49]) was in line with the findings from COV3001. These data suggest that the increase in immunogenicity following a second dose of Ad26.COV2.S (see Section 3.2.1) coincides with an increase of protection.

Vaccine efficacy against moderate and severe COVID-19 at least 14 days after 2 doses of Ad26.COV2.S was consistent among age groups as well as participants with and without co-morbidities. Regional differences in VE were observed. In the US VE (95% CI) against moderate to severe/critical COVID-19 as of 14 days after the second dose was 93.7% (58.45;99.85). Observed VE in other regions was lower (60.0%-68.8%) which was possibly driven by reduced VE against certain SARS-CoV-2 variants.

In the study, based on preliminary analysis of sequencing results (68.0% cases with available sequence) Alpha (B.1.1.7) and Mu (B.1.621) had sufficient cases available for analysis and interpretation of the data. Post-dose 1, VE for these variants was similar as observed in COV3001, and the second dose of Ad26.COV2.S increased the vaccine efficacy for both variants (see Table 7). There were insufficient Delta cases for meaningful analysis Of the 13 Delta cases in the entire double blinded study phase (with onset day as of Day 1), only 3 cases had an onset at least 14 days after the second vaccination (2 in the Ad26.COV2.S group and 1 in the placebo group).

Table 6: Vaccine Efficacy – Final Analysis COV3009

	Number of cases as of 14 days after 2nd dose VE 14 days after 2nd dose	95% CI*
Moderate and severe/critical COVID-19	14 vs 52 75.2%	(54.55; 87.30)*
All SARS-CoV-2 infections	60 vs 113 51.1%	(29.50; 66.45)*
Symptomatic COVID-19 severity	14 vs 53 75.6%	(55.48; 87.52)
Mild	0 cases vs 1 case -	-
Moderate	14 vs 44 70.7%	(45.46; 85.15)
Severe/ critical	0 vs 8 100.0%	(32.62; 100.00)*
Asymptomatic SARS-CoV-2 infection	40 vs 56 34.2%	(-6.44; 59.78)*
Req. Medical intervention	0 cases vs 5 cases -	-
COVID-19 related deaths[a]	0 cases vs 1 case -	-

Analysis set: per protocol: 7,484 and 7,008 participants in the Ad26.COV2.S and placebo group, respectively; risk set: 6,024 and 5,615 participants in the Ad26.COV2.S and placebo group, respectively
The risk set are all subjects of the Per Protocol Set excluding subjects that had a positive PCR test between day 1 and day 14
* The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.
[a]A fatality is covid-19 related if it is covid-related according to the adjudication committee or it has a fatal adverse event that is covid-19 related after the onset of a covid-19 episode with at least 1 documented PCR
NE: Not Evaluable

Table 7: Vaccine Efficacy by Variants 14 days post dose 1 (PPFD set) and 14 days post dose 2 (PP set)– Final Analysis COV3009

	Day 15-Day 56		Day ≥71	
	Point estimate	95% CI	Point estimate	95% CI
All	67.0%	(53.6;77.0)	75.2%	(54.6;87.3)
Alpha (B.1.1.7)	71.6%	(43.2;86.9)	94.2%	(62.9;99.9)
Mu (B.1.621)	43.9%	(-43.4;79.6)	63.1%	(-27.9;91.6)

3.2. Immunogenicity – Booster at 2 Months

3.2.1. COV3009 - Ad26.CoV2.S Booster at 2 Months

Analysis of the immunogenicity results was based on the PPI population consisting of all randomized and vaccinated participants for whom immunogenicity data were available.

It should be noted that results described in this report are based on partial data as not all samples for the different timepoint have been analyzed. Results should therefore be interpreted with caution.

Samples analyzed per timepoint:

- Day 1: 394 out of 445 samples
- Day 29: 351 out of 385 samples
- Day 57: 342 out of 384 samples
- Day 71: 371 out of 381 samples

Participants were equally distributed across the 2 age groups (18 to 59 years and above 60 years of age) and sexes. The majority of participants were White or Black/African American (72.2% and 16.4%), respectively. The majority of participants were non-Hispanic or Latino (85.6%).

S binding antibody concentrations and responder rates increased both after the first and second vaccination (see Table 8)[2]. The geometric mean increase was 7.2-fold from baseline to Day 29, 10.4-fold from baseline to Day 57, and 40.5-fold from baseline to Day 71 or 4.7-fold from Day 57 (pre-dose 2) to Day 71.

Similar S binding antibody levels were observed across different regions (Europe and the US). In participants ≥60 years of age with and without comorbidities, the geometric mean concentrations (GMCs) at Day 29 are generally lower compared to participants ≥18 to <60 years of age with and without comorbidities. As of Day 57, the GMCs in participants ≥60 years of age with and without comorbidities are generally comparable to those from participants ≥18 to <60 years of age with comorbidities. At Day 71, responder rates reached 100% in both age groups and comorbidity strata.

[2] In the placebo group, 5 responders were observed, and investigations are ongoing to understand these responses, for instance whether these participants experienced SARS-CoV-2 infection in the first 4 weeks after vaccination.

Table 8: SARS-CoV-2 S Binding Antibodies (ELISA Unit (EU)/mL): Descriptive Statistics; Immuno Set PPI (Study VAC31518COV3009)

	Ad26 5e10 vp Double-Blind	Placebo Double-Blind
Analysis set: Immuno Set PPI Population	187	166
Baseline		
N	157	149
Geometric mean (95% CI)	< LLOQ (< LLOQ; < LLOQ)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	7 (4.5%) (1.8; 9.0)	2 (1.3%) (0.2; 4.8)
Day 29		
N	140	124
Geometric mean (95% CI)	367 (295; 456)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	131 (93.6%) (88.1; 97.0)	7 (5.6%) (2.3; 11.3)
Geometric mean increase (95% CI) from Baseline	7.2 (5.8; 8.9)	1.1 (1.0; 1.2)
Responders n/N* (%) (95% CI)	113/123 (91.9%) (85.6; 96.0)	5/112 (4.5%) (1.5; 10.1)
Day 57		
N	150	111
Geometric mean (95% CI)	518 (422; 635)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	143 (95.3%) (90.6; 98.1)	4 (3.6%) (1.0; 9.0)
Geometric mean increase (95% CI) from Baseline	10.4 (8.4; 12.8)	1.1 (1.0; 1.3)
Responders n/N* (%) (95% CI)	125/132 (94.7%) (89.4; 97.8)	3/102 (2.9%) (0.6; 8.4)
Day 71		
N	78	62
Geometric mean (95% CI)	2220 (1794; 2748)	< LLOQ (< LLOQ; < LLOQ)
Positive sample n (%) (95% CI)	78 (100.0%) (95.4; 100.0)	5 (8.1%) (2.7; 17.8)
Geometric mean increase (95% CI) from Baseline	40.5 (32.6; 50.2)	1.3 (0.9; 1.8)
Geometric mean increase (95% CI) from Pre-Dose 2	4.7 (3.8; 5.7)	1.1 (0.9; 1.4)
Responders n/N* (%) (95% CI)	68/68 (100.0%) (94.7; 100.0)	4/53 (7.5%) (2.1; 18.2)

Key: CI = confidence interval
N = number of subjects with data
N* = number of subjects with data at baseline and at that time point.
Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample and Responders.
Positive sample refers to a quantifiable response (sample interpretation).
The assay status is: validated.

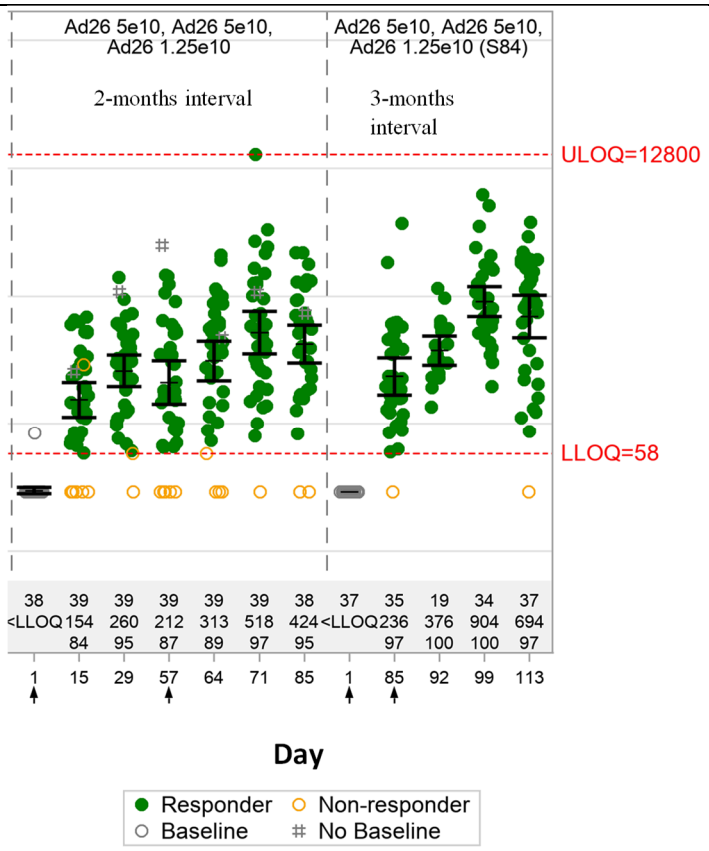
[TIRHUM21.RTF] [VAC31518\VAC31518COV3009\DBR_IA1\RE_IA1\PROD\TIRHUM21.SAS] 22SEP2021, 04:49

3.2.2. COV2001: - Ad26.CoV2.S Booster at 2-3 Months

Participants >18 years of age received a 2nd dose of Ad26.COV2.S (5×10^{10} vp) either at Day 57 (2 months; Group 1) or at Day 85 (3 months; Group 9). Pre-dose 2, GMTs, fold increase from baseline, and responder rates were comparable for the 56-day interval (Group 1) and 84-day interval (Group 9) regimens. At the 14 days and 28 days post-dose 2 time points, a trend was observed for higher numerical GMT values and geometric mean increases (GMIs) from baseline in the 84-day interval group [GMIs from pre-dose of 3-fold; 14 days and 28 days post-dose 2] compared to the 56-day interval group (GMIs from pre-dose 2 of 2-fold; 14 days and 28 days post-dose 2) (Figure 13). Similar results were obtained when analyzing binding antibody responses. Comparable GMCs and responder rates for participants aged ≥65 years and participants aged 18-55 years were observed for the 56-day interval. Higher GMCs and similar responder rates were observed in participants aged ≥65 years compared to participants aged 18-55 years for the 85-day interval.

In summary, a 2nd dose of Ad26.COV2.S at the 5×10^{10} vp dose level, either 2 or 3 months after dose 1, induced an increase in humoral immune responses, which were durable up to at least Day 85 (post dose 1) after vaccination, suggesting that a booster dose 6 months after primary vaccination may be beneficial to increase immune responses.

Figure 13: SARS-CoV-2 neutralization wild type VNA - VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Adult Subjects, Group 1239; Per Protocol Immunogenicity Set (Study VAC31518COV2001)



Note: Geometric mean titers with 95% CI shown in the figure.
Note: Ad26 1.25e10: Ad26.COV2.S 1.25x10 [10] vp; Ad26 5e10: Ad26.COV2.S 5x10 [10] vp.
The status of wtVNA assay is qualified. The assay range may change as the assay becomes validated.

Adapted from: [GIRHUM01-G1239.RTF] [VAC31518\VAC31518COV2001\DBR_ADULT_IA2_SEQUESTERED\RE\PROD\GIRHUM01-G1239.SAS] 11AUG2021, 05:01

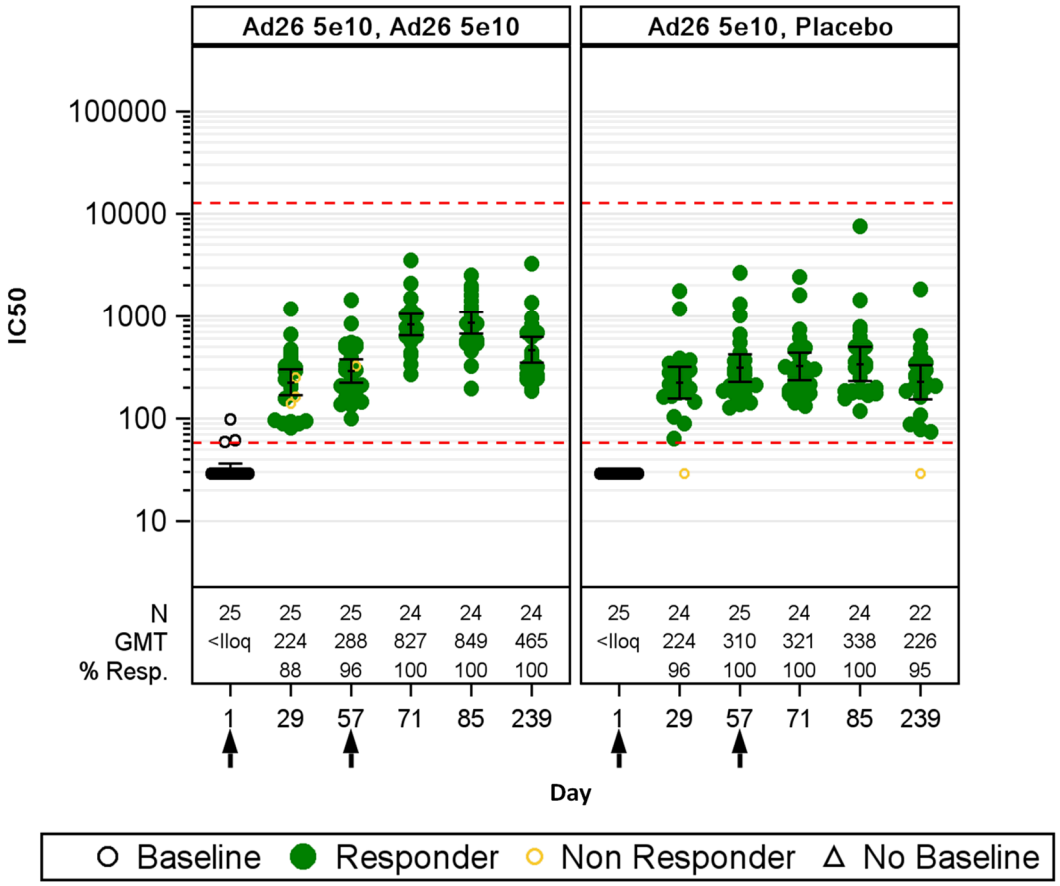
3.2.3. COV1001 - Ad26.CoV2.S Booster at 2 months

It is important to note that due to the study pause, blood draws for immunogenicity were delayed for the majority of Cohort 3 participants from Day 57 onwards in study COV1001. Collection of samples from Day 57 onwards, within the defined per protocol visit windows, was only possible in 15 sentinel participants (N=3 per group). Therefore, Cohort 3 data presented below are based on the full analysis set (FAS) instead of the per-protocol immunogenicity (PPI) set, ie, samples collected out of window from Day 57 onwards.

A sensitivity analysis on the FAS for Cohort 3, excluding the 15 sentinels is shown in Figure 15. For the majority of participants in Cohort 3, the actual timing of Day 57 blood draws ranged from 86 to 107 days post-vaccination (median visit = Day 87). Therefore, the Day 57, Day 71, Day 85 and Day 239 timepoints referred to in Figure 14 are referred to as 'Day 87, Day 100, Day 114 and Day 268' in Figure 15.

Cohort 1a (18 to 55 years of age; Figure 14) and Cohort 3 (≥65 years of age; Figure 15) Group 1 participants who received a 2nd dose of Ad26.COV2.S (5×10^{10} vp) at Day 57 (2 months; Cohort 1a) or at Day 87 (3 months: Cohort 3) had a substantial increase in humoral neutralizing responses, with durable responses up to Day 85 (1 month post-dose 2 [Day 114 Cohort 3]), representing GMIs from baseline of >14-fold for both age groups. The higher fold increase seen in the ≥65 years of age participants is most likely due to the longer interval between the primary and the booster dose. Likewise, antibody binding responses also increased after the 2nd dose of Ad26.COV2.S and remained stable up to 28 days post-dose 2 (Day 85 [Day 114 for Cohort 3]). Antibody binding responses declined 6 months post-dose 2 (Day 239; only assessed in Cohort 1a). Neutralizing and binding antibody responses after the second dose were shown to be higher than responses in human convalescent serum (Sadoff 2021).

Figure 14: SARS-CoV-2 Neutralization Wild Type VNA - VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Cohort 1a (18 to 55 years of age); Per Protocol Immunogenicity Set (Study VAC31518COV1001)

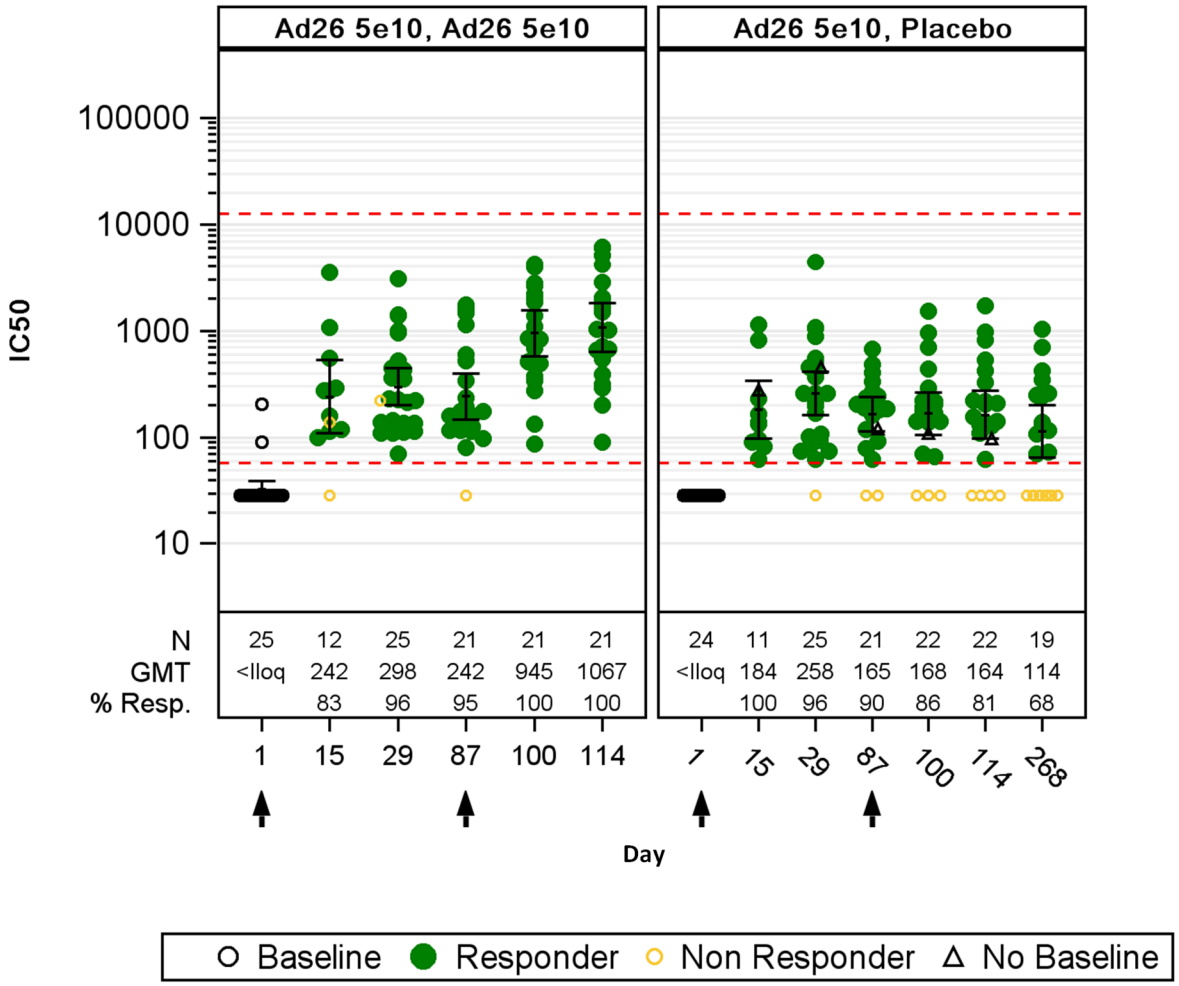


LLOQ=58, ULOQ=12800

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

Adapted from: [girhum61-c1a.rtf] [Findings/is/pgm/is21.sas] 25AUG2021, 4:31:04PM SAS 9.4

Figure 15: SARS-CoV-2 neutralization wild type VNA - VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Cohort 3 (≥65 years of age); Full Analysis Set (Study VAC31518COV1001)



LLOQ=58, ULOQ=12800

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

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

3.2.4. COV1002 - Ad26.CoV2.S Booster at 2 months

Cohort 1 (≥20 to ≤55 years of age) and Cohort 2 (≥65 years of age) participants who received a 2nd dose of Ad26.COV2.S (5×10^{10} vp) at Day 57 (2 months) had a substantial increase in humoral responses, with responses at Day 71 (14-day post-dose 2) representing GMIs from baseline of around 18-fold and ~9-fold, respectively. Responses were generally durable up to at least Day 85 (3 months) after vaccination.

3.3. Immunogenicity – Booster at 6 Months

3.3.1. COV1001 - Ad26.CoV2.S Booster at 6 months

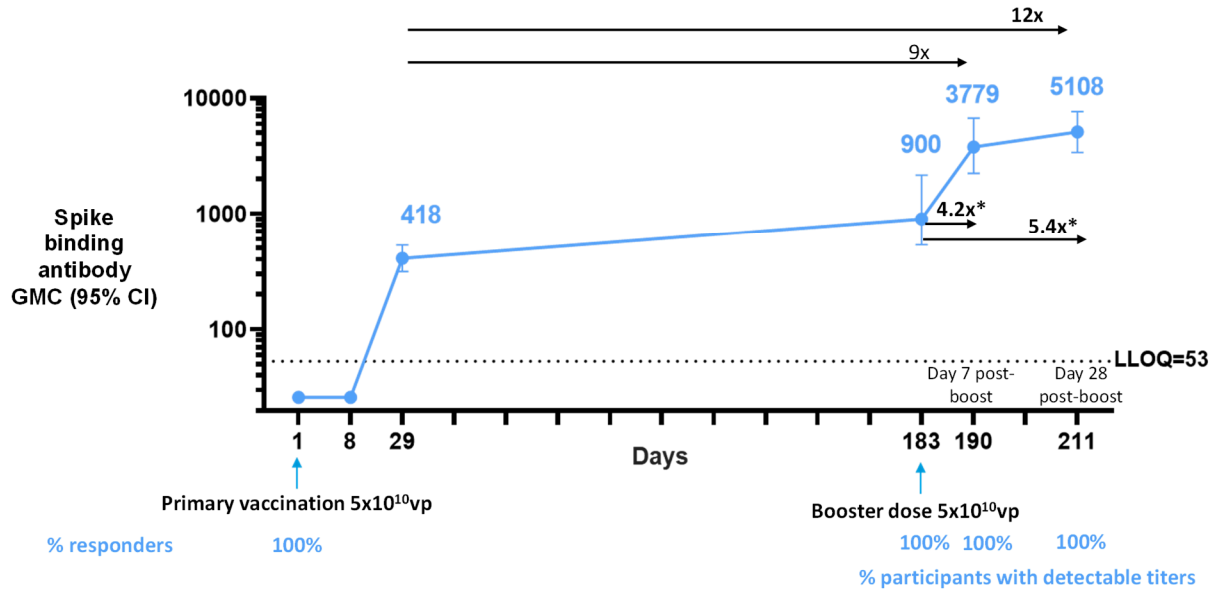
In Cohort 2a (Group 2) of study COV1001, immunogenicity of a booster dose after the primary vaccination regimen was evaluated in healthy adults aged ≥18 to ≤55 years. Participants received Ad26.COV2.S at the selected dose level of 5×10^{10} vp as the first dose and received Ad26.COV2.S at a dose level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

Boosting with Ad26.COV2.S (5×10^{10} vp) 6 months after primary vaccination induces a substantial and rapid increase of humoral immune responses (see Figure 16).

- 7 days after the booster (Day 190), binding antibody concentrations demonstrated a substantial and rapid increase to 3,779 (N=17), representing a GMI from pre-booster levels of 4.2-fold. Similarly, neutralizing antibodies (psVNA) increased 3.5-fold compared to pre-boosting (GMT of 156 versus 33 on Day 190 and Day 183, respectively).
- 28 days after the booster, (Day 211), a further increase in binding antibody concentrations to 5,108 (N=15) was observed, representing a GMI from pre-booster levels of 5.4-fold. Similarly, neutralizing antibodies (psVNA) increased 5.0-fold compared to pre-boosting (GMT of 241 versus 33 on Day 211 and Day 183, respectively).
- In participants who did not receive a booster dose 6 months after primary vaccination, GMC and responder rates remained stable between Day 29 and Day 183 and decreased slightly at Day 190 and Day 211 compared to the Day 29 responses, confirming the previously described immunogenicity results on the durability of the response induced by a single dose of Ad26.COV2.S (see Section 2.1.2).

A 5 x 10^{10} vp booster dose at 6 months elicited a rapid increase in binding Abs 7 days post boost, compared to immediate pre-boost levels and compared to Day 29 post dose 1 levels in 18–55 yo participants, exceeding levels of human convalescent sera reported earlier by about 4-fold (Sadoff 2021).

Figure 16: Durability of Spike Binding Ab Response up to 6 Months Post Single Ad26.COV2.S Dose and Booster Dose Impact, 18-55 Year-old Participants in COV1001



Sadoff 2021
LLOQ=lower limit of quantitation
*GMI=geometic mean increase

Moreover, a post-hoc NI analysis was performed on the 17 participants from COV1001 Cohort 2a/group 2. This post hoc analysis calculated the fold increase in the ELISA assay (Nexelis) and the psVNA assay (Janssen Vaccines Discovery) from 28 days post dose 1 to 7 days post booster dose (Day 190) and from 28 days post dose 1 to 28 days post booster dose (Day 211). While the study did not include a pre-specified non-inferiority objective, the results of this post-hoc analysis can be interpreted in relation to standard non-inferiority criteria such as a lower limit of the 95% confidence interval being above 0.67. The calculated fold-increases, were:

- For the ELISA assay: 9.04 (N=17; 95% CI: 5.86; 13.96) and 11.99 (N=15; 95% CI: 7.92;18.16) 7 and 28 days post booster dose, respectively.
- For the psVNA assay: 7.20 (N=17; 95% CI: 4.80; 10.81) and 11.01 (N=15; 95% CI: 7.96; 15.21) 7 and 28 days post booster, respectively. Note that values below the LOD at 28 days post-dose 1 were imputed with the LOD.

The lower limit of each of these CIs was above 1, thereby also meeting standard non-inferiority criteria such as a lower limit of the 95% CI above 0.67, for both assays at both timepoints.

3.3.2. COV2001 – Anamnestic Response

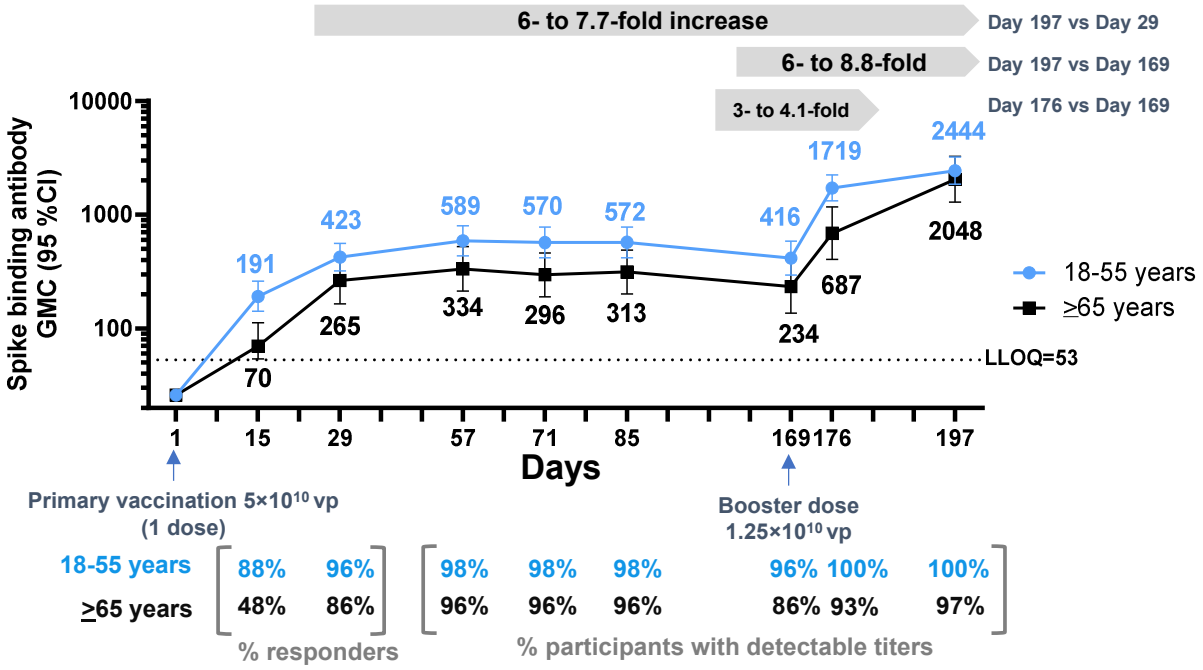
Immunogenicity data from participants who received the Antigen Presentation 6 months post dose 1 are available from study COV2001. Participants received Ad26.COV2.S at the selected dose level of 5×10^{10} vp as the first dose and received Ad26.COV2.S at a dose level of 1.25×10^{10} vp as the Antigen Presentation 6 months post vaccination (Group 5).

At Day 176 (7 days post-antigen presentation), a steep increase in binding antibody responses was observed in the 5×10^{10} vp, placebo (PL) (56-day) vaccine group (>96% responder rates and GMCs of 1,197). At Day 197 (28 days post-antigen presentation), binding antibody responses increased further to GMCs of 2,272. Compared to the Day 29 levels following the initial immunization, a 6-fold increase at 28 days post-antigen presentation in the 5×10^{10} vp, PL (56-day) vaccine group was observed (Figure 17).

Up to 7 days after $1.25x10^{10}$vp antigen exposure/low dose boost, participants aged ≥65 years had lower GMCs and comparable responder rates compared to participants aged 18-55 years while 28 days after antigen exposure/low dose boost, comparable GMCs and responder rates were observed between both age groups.

In summary, these results demonstrate that a lower dose (1.25×10^{10} vp) of Ad26.COV2.S elicits a rapid anamnestic response, 7 days and 28 days after antigen exposure/low dose boost. Additionally, these results are supportive for a booster dose 6 months post-dose 1 to maintain substantial immune responses over time.

Figure 17: Durability of SARS-CoV-2 S binding antibodies (ELISA Unit (EU)/mL) Following Boosting with 1.25×10^{10} vp at 6 months (Study VAC31518COV2001)



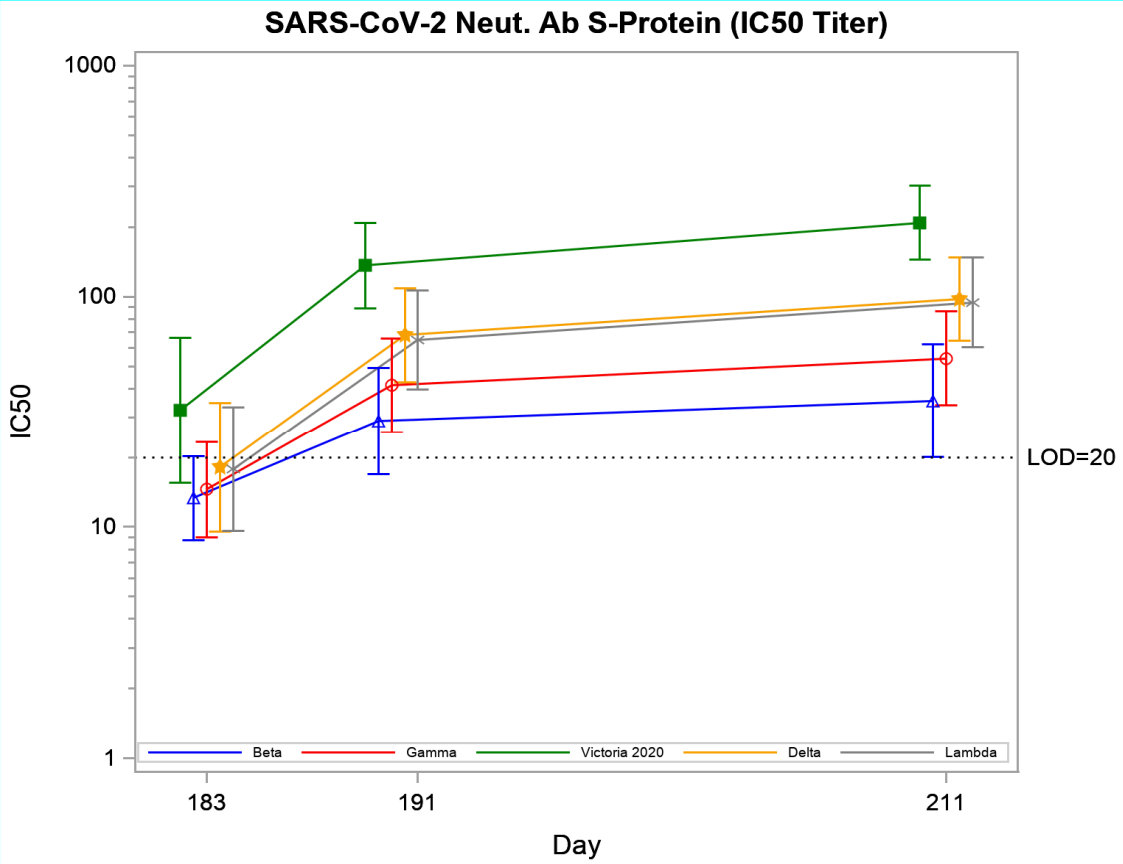
3.4. Immunogenicity of a 2-dose Vaccination Against Variants of Concern

Samples from a subset of Cohort 2a participants from study COV1001 who had received a 6-month booster vaccination (n=17) were measured for neutralizing antibodies against the SARS-CoV-2 Beta, Gamma (P.1 lineage), Delta, and Lambda (C.37 lineage) variants by a psVNA conducted by JBDA.

Graphical representation of neutralizing responses (geometric means) to the original strain and to the 4 variants, as measured by the developed Janssen Bioassay Development and Automation (JBDA) psVNA, prior to booster and at Day 183 and Day 190 are shown in Figure 18. Post boost, neutralizing antibodies to the original strain were numerically higher than those seen against the variants, although some overlap of the 95% CIs was seen with both the Delta and Lambda variants at Day 191.

This exploratory analysis showed that neutralizing antibodies against the Beta variant were numerically lower than those against the other variants, with some overlap of the 95% CIs at the post boost timepoints. Neutralizing antibodies against the Delta and Lambda variant were comparable, and numerically higher than those against the Gamma and Beta variants, although overlap of the 95% CIs was apparent.

Figure 18: Pseudovirion Neutralization (IC50) of Victoria/1/2020 Strain, Beta Variant, Gamma Variant, Delta Variant and Lambda Variant, Cohort 2a (N=17); PPI Set, Active Vaccine Booster Group (VAC31518COV1001)



Geometric mean values with 95% confidence intervals are shown. The JBDA psVNA assay is 'developed'

Samples were also measured for binding antibodies against the SARS-CoV-2 original strain, Beta variant and Delta variant. This analysis utilized developed ELISAs conducted by JBDA. Binding rapidly increased after a booster dose of 5×10^{10}vp of Ad26.COV2.S.

By Day 190 (7 days post booster) for the Beta variant, binding antibodies remained at 100% and the mean EC_{50} was now 3.04, representing a mean increase from pre-booster levels of 0.73. For the Delta variant, binding antibodies also remained at 100% and the mean EC_{50} was now 3.02, representing a mean increase from pre-booster levels of 0.67. For both variants, these responses remained stable to Day 211, the last timepoint tested. A high correlation between the Nexelis ELISA and the JBDA ELISA was seen at all the timepoints (Spearman values >0.90). This suggests that despite differences in the S protein from the Beta or Delta variant and reference strain (Victoria/1/2020), the Nexelis S-ELISA could potentially be used as a surrogate for the Beta and Delta variant S ELISAs.

3.5. Impact of Neutralizing Antibodies Against the Ad26 Vector

Although experience with the Ad26 vaccine platform for other vaccines have not indicated this, in theory, neutralizing antibodies to the Ad26 vector generated post-dose 1 may have the potential to negatively impact responses to Ad26.COV2.S post-dose 2. Therefore, neutralizing antibodies to the Ad26 vector were measured in study COV1001 (Cohort 1a; Group 1 and Group 3; ie, 2 doses of Ad26.COV2.S at the 5×10^{10} vp and 1×10^{11} vp dose levels, respectively, with a 56-day interval), by the Ad26 VNA at baseline and prior to second vaccination on Day 57 only.

Overall, in the majority of participants, the induction of Ad26 antibodies at Day 57 did not appear to prevent further increases in SARS-CoV-2 neutralizing antibodies after a second dose of Ad26.COV2.S, at the 5×10^{10} vp (or higher) dose level. Correlation analysis of Ad26 neutralizing antibodies pre-dose 2 compared to SARS-CoV-2 neutralizing antibodies post-dose 2 showed a poor correlation between the 2 variables. For other studies, similar increases in binding and neutralizing antibodies were observed after a second dose at Day 57, further supporting these data.

3.6. Correlation Between Neutralizing, Binding, and Functional Antibody Responses

Correlation Between Neutralizing Antibodies and Binding Antibodies

In Study COV1001 (Cohorts 1a and 3), for the reference strain, neutralizing antibody titers (IC_{50}) demonstrate high correlation with binding antibody concentrations (EU/mL). The correlations for Cohort 1a Day 29 and Day 239 are presented in Appendix 4 Figure 25. The correlation plot for Cohort 3 is presented in Appendix 4 Figure 26.

The Spearman correlation between the 2 assays was ≥0.70 independent of the timepoint (Day 29, Day 71, Day 85, and Day 239), hence, ELISA could be used as a surrogate of the neutralizing immune response, ie, an increased binding antibody response likely reflects an increased neutralizing response.

Additionally, at any timepoints post-dose 1 and 2 (independently of the dose interval), ELISA and VNA results highly correlated, across studies and age group.

Correlation Between Functional Antibody Responses and Neutralizing or Binding Antibody Reponses

In study COV1001 (Cohorts 1a, 1b, and 3), antibody-dependent cellular phagocytosis of SARS-CoV-2 trimeric Spike antigen was measured by an antibody-dependent cellular phagocytosis (ADCP) assay. Fc-mediated functional antibodies were elicited by a single dose of Ad26.COV2.S and further increased by a second dose. Correlation analysis demonstrated a positive correlation between ADCP (phagocytic score) and neutralizing antibody titers (IC_{50}) at Day 29 and Day 71, with Spearman correlation values ≥0.75 (Appendix 4 Figure 27). A strong positive correlation between phagocytic score and binding antibody titers (EU/mL) at Day 29 and Day 71 was also demonstrated (Spearman correlation values >0.85) (Appendix 4 Figure 28).

Altogether, these results for ADCP highly correlated with neutralizing and binding antibody results, hence, these fc-mediated antibody functions are expected to be also increased with a booster dose.

4. SAFETY OF AD26.COV2.S

4.1. Overview of Safety Profile of Ad26.COV2.S Given as a Single Dose

4.1.1. Overview of COV3001 Safety Data

The most extensive safety information of the single-dose Ad26.COV2.S regimen (5×10^{10} vp dose level) is available from the pivotal Phase 3 study COV3001 on 43,788 participants ≥18 years of age (21,898 participants who received Ad26.COV2.S and 21,890 participants who received placebo). The primary analysis of this study (cut-off date 22 January 2021) 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 and included data from the Safety subset (ie, a subset of the FAS) for the analysis of solicited and unsolicited adverse events (AEs) and data from the FAS for the analysis of medically attended adverse events (MAAEs), deaths, other serious adverse events (SAEs), and AEs leading to study/vaccine discontinuation. The Safety subset included 3,356 participants who received Ad26.COV2.S and 3,380 participants who received placebo. The final analysis of the double-blind phase of this study (cut-off date: 09 July 2021) confirms the established safety profile of Ad26.COV2.S:

- At the time of the final analysis of the double-blind phase, the median follow-up after vaccination was 123 days and 11,290 (25.8%) participants in the FAS had at least 6 months (defined as 24 weeks) of double-blind follow-up. Results indicate that a single dose of Ad26.COV2.S at a dose level of 5×10^{10} vp has an acceptable safety and reactogenicity profile in adults ≥18 years of age, including adults ≥60 years of age. No significant safety issues were identified. In general, lower reactogenicity was observed in older adults compared to younger adults in this analysis.
- As most participants had completed follow-up of solicited and unsolicited AEs for 7 and 28 days post-vaccination, respectively, at the time of the primary analysis, conclusions on reactogenicity remain unchanged in the final analysis.
- In the double-blind phase, 83 participants with one or more fatal AEs were reported: 28 in the Ad26.COV2.S group and 55 in the placebo group. During the entire study, 100 participants with one or more fatal AEs were reported, of which 40 occurred in participants who received Ad26.COV2.S. Four deaths were reported after open-label vaccination with Ad26.COV2.S. One of these events was considered related to the study vaccine by the investigator. This participant was reported to have a Grade 4 pulmonary embolism 57 days after open-label vaccination with Ad26.COV2.S.
- Of all participants receiving Ad26.COV2.S during the entire study, 436 (1.2%) were reported with 1 or more SAE. In the double-blind phase, 223 (1.0%) participants reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared to 265 (1.2%)

participants in the placebo group. A total of 14 (0.1%) participants reported SAEs associated with COVID-19 in the Ad26.COV2.S group, compared to 100 (0.5%) participants in the placebo group.

- During the entire study, 19 participants reported a total of 21 SAEs which were considered to be related to the study vaccine by the investigator: 19 events (reported by 18 participants) in the Ad26.COV2.S group (3 cases of ischemic stroke, 2 cases of Bell's Palsy, 2 cases of pulmonary embolism, 2 cases of deep vein thrombosis, Guillain- Barré syndrome (GBS), venous thrombosis limb, retinal vein thrombosis, atrial fibrillation, pericarditis, complex regional pain syndrome, post vaccination syndrome, hypersensitivity, headache and asthma) and 2 events (reported by 1 participant) in the placebo group (Epstein-Barr virus infection and atrial flutter).
- 1 SAE of thromboembolic event with thrombocytopenia (venous transverse sinus thrombosis and cerebral hemorrhage) reported following administration of Ad26.COV2.S was confirmed as thrombosis with thrombocytopenia syndrome (TTS) meeting both Level 1 criteria using the Brighton Collaboration level of certainty and the CDC definition for a tier 1 TTS case and could therefore be confirmed as TTS according to both case definitions.
- The following AEs of interest had a numerical imbalance between the Ad26.COV2.S and placebo group: tinnitus, seizures, and embolic and thrombotic events. Tinnitus was considered an adverse reaction. Further review of events of seizure and embolic and thrombotic events revealed that the majority had predisposing, underlying medical conditions, and these were not considered safety concerns upon further evaluation; the number of events contributing to the imbalance was small, and these imbalances were not observed in COV3009 (see Section 4.2.2.9 for details). A limited number of MAAEs of at least Grade 3, none of which were considered as a safety issue, and no events of anaphylaxis were reported in the Ad26.COV2.S group in COV3001.

All remaining participants in COV3001 (estimated >30,000 participants) will be offered an Ad26.COV2.S 5×10^{10} vp booster, and will be followed up in the open-label phase for 1 year post-booster).

4.1.2. Overview of Postmarketing Safety Data

Since the EUA by FDA, and as of 31 August 2021, an estimated 33.5 million doses of Ad26.COV2.S (5×10^{10} vp) have been administered in a postmarketing setting worldwide (an estimated 14.3 million doses in the US, 13.6 million doses in the European Economic Area, and 5.6 million doses in the rest of the world (CDC 2021f, ECDC 2021d, KDCA 2021, Ministério da Saúde 2021). Based on postmarketing surveillance data accruing since the emergency use authorization, TTS, GBS, and Capillary Leak Syndrome (CLS) have been identified as new safety concerns for Ad26.COV2.S and added to the US prescribing information.

Thrombosis with Thrombocytopenia Syndrome

As of a cut off of 24 August 2021, cases of TTS with a reporting frequency of 5-6 per million doses administered have been received in the company safety database from worldwide sources.

The reporting frequency of the cases received from worldwide sources and meeting the CDC criteria for TTS (Tier 1 [Shimabukuro 2021]) was approximately 2 per million doses administered. The majority of the cases (69%) were reported from the US and in age groups below 65 years (82.6%), 45% in males and 55% in females where gender and age were reported. The mean and median time-to onset (TTO) of the event was 16.5 and 12 days, respectively.

Guillain-Barre Syndrome

Postmarketing AE reports with events of GBS have been received in the company safety database with a reporting frequency of 7-8 per million doses administered, with the majority of the cases (64.2%) reported from US. The annual background incidence of GBS is estimated at 4.15 per 100,00 persons (Lee 2020). Based on a 42-day risk window for GBS, this approximates to 4-5 cases per million. The mean and median ages were 53.1 and 55 years, respectively with the range of 22 to 87 years, and involved more males (63.6%) than females (36.3%). The mean and median TTO of the event after vaccination was 36 days and 14 days, respectively.

Capillary Leak Syndrome

Very rare cases of CLS (0.21 per million doses administered) have been reported from postmarketing sources, some of them with a prior history of CLS and with fatal outcomes. The mean and median TTO was 1.3 days and 1 day, respectively.

The US prescribing information has been updated for these adverse reactions and the benefit-risk profile of Ad26.COV2.S post-EUA remains favorable. The sponsor has a robust pharmacovigilance system for safety monitoring of AEs from post marketing sources and will continue to monitor the safety profile of booster doses through routine pharmacovigilance activities and through the studies per postmarketing commitments/requirements (Section 5).

4.2. Overview of Safety Profile of Ad26.COV2.S Given as a Booster Dose

4.2.1. Introduction and Methodology

A total of 9,379 participants have received 2 doses of Ad26.COV2.S at the 5×10^{10} vp dose level in clinical studies (Table 9). Of these, 2,383 participants were aged ≥60 years.

Table 9: Number of Adult Participants who Received a Primary Dose and Booster of Ad26.COV2.S at the $5x10^{10}$ vp Dose Level in Clinical Studies

	2-month interval	3-month interval	6-month interval	≥6-month interval	All intervals
COV1001	190	77*	19	0	286
COV1002	91	0	0	0	91
COV2001	137*	51	0	0	188
COV2008**	0	0	0	159	159
COV3009	8655	0	0	0	8655
Total	**9073**	**128**	**19**	**159**	**9379**

Cut-off dates were 21 July 2021 for COV1001, 28 December 2020 for Cohort 1 of COV1002, 22 February 2021 for Cohort 2 of COV1002, 11 May 2021 for COV2001, and 25 June 2021 for COV3009. For COV2008, data were extracted from the database on 7 September 2021.

* In COV1001, some participants received the second dose with a 3-month rather than the scheduled 2-month interval because of a study pause. In COV2001, some participants received the second dose with a 2-month rather than the scheduled 1-month interval because of a study pause.

** In COV2008, 370 participants who received Ad26.COV2.S in study COV3001 were randomized in a 3:3:1 ratio to receive a second dose of Ad26.COV2.S at a dose level of 5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp . Study data are still blinded. This number is estimated based on the number of randomized participants and randomization ratio.

Unless otherwise specified, AEs were collected as follows:

- Solicited local and systemic AEs (reactogenicity), from the day of vaccination until 7 days after each vaccination:
    - Solicited local AEs: injection site pain/tenderness, erythema, and swelling.
    - Solicited systemic AEs: fatigue, headache, nausea, myalgia, and pyrexia/fever (body temperature ≥38°C/100.4°F).
- Unsolicited AEs, from the day of vaccination until 28 days after each vaccination.
- SAEs, including deaths, and any AEs leading to study discontinuation from the day of first vaccination until the end of the study.
- Phase 3 studies: 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.
- Following the identification a safety signal for very rare events of TTS in postmarketing data, TTS was considered an AESI in clinical studies. A thrombotic event or thrombocytopenia (defined as platelet count below 150,000/µL [Brighton 2021]) alone was considered a suspected AESI for further investigation.
- In addition, based on clinical and postmarketing data, publications, and regulatory interactions, additional AEs of interest were selected for further evaluation in Phase 3 studies.

4.2.2. Overview of COV3009 Safety Data

4.2.2.1. Study Population and Vaccine Exposure

The most extensive safety information for 2 doses of Ad26.COV2.S at 5×10^{10} vp is available from the Phase 3 study COV3009. This study includes 31,300 participants, of whom 8,655 participants received a booster dose of Ad26.COV2.S in the double-blind phase. The results of a safety analysis for the double-blind phase are presented below.

At the data cutoff for this analysis (25 June 2021), 71.2% and 28.4% of participants had completed 2 months of follow-up after the first and booster vaccinations, respectively. Summaries of solicited and unsolicited AEs are based on the Safety Subset (ie, a subset of the FAS), which included 6,068 participants (3,016 in the Ad26.COV2.S group and 3,052 in the placebo group). Summaries of deaths, SAEs, MAAEs, AESIs, and AEIs are based on the FAS (31,300 participants; 15,708 in the Ad26.COV2.S group and 15,592 in the placebo group).

Overall in the FAS, 76.4% of participants were white and 52.6% of participants were male. The median age was 53 years (range: 18; 99 years) and 35.9% of participants were ≥60 years of age. Demographic characteristics were similar in the Safety subset.

4.2.2.2. Solicited Adverse Events

4.2.2.2.1. Solicited Local Adverse Events

The frequency of solicited local AEs after each vaccination is presented in Table 10. The frequency of solicited local AEs for the younger adult (18-59 years) and older adult (≥60 years) groups is presented in Figure 19. A general trend for lower reactogenicity was observed in older adults.

In the Ad26.COV2.S group, solicited local AEs were reported for 55.6% and 57.5% of participants post-dose 1 and post-booster, respectively, with vaccination site pain being most frequently reported after each dose (54.2% and 56.3%). Most solicited local AEs were Grade 1 or Grade 2 in severity. The frequency of Grade 3 solicited local AEs was low and no Grade 4 events were reported. Reactogenicity was transient, with a median duration of 2-3 days after vaccination with Ad26.COV2.S.

Table 10: Number of Subjects with Local Solicited Adverse Events by Derived Term; Safety Subset (Study VAC31518COV3009)

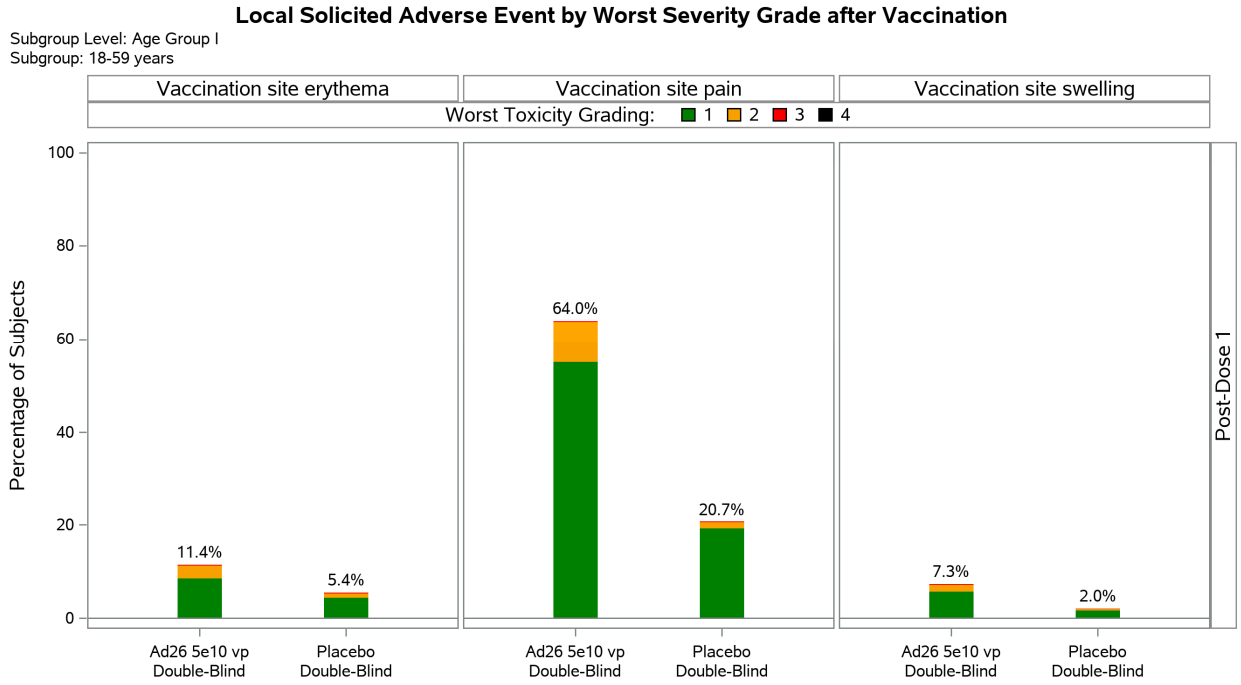
	Ad26 5e10 vp Double-Blind	Placebo Double-Blind
Analysis set: Safety Subset	3016	3052
Post-dose 1	3015	3052
Subjects with 1 or more Local AEs		
Any	1676 (55.6%)	653 (21.4%)
Grade 3	9 (0.3%)	6 (0.2%)
Vaccination Site Erythema		
Any	263 (8.7%)	142 (4.7%)
Grade 3	2 (0.1%)	1 (<0.1%)
Vaccination Site Pain		
Any	1634 (54.2%)	556 (18.2%)
Grade 3	3 (0.1%)	4 (0.1%)
Vaccination Site Swelling		
Any	167 (5.5%)	52 (1.7%)
Grade 3	4 (0.1%)	1 (<0.1%)
Post-booster	1559	1425
Subjects with 1 or more Local AEs		
Any	896 (57.5%)	252 (17.7%)
Grade 3	10 (0.6%)	3 (0.2%)
Vaccination Site Erythema		
Any	128 (8.2%)	56 (3.9%)
Grade 3	7 (0.4%)	2 (0.1%)
Vaccination Site Pain		
Any	877 (56.3%)	225 (15.8%)
Grade 3	3 (0.2%)	1 (0.1%)
Vaccination Site Swelling		
Any	88 (5.6%)	18 (1.3%)
Grade 3	2 (0.1%)	0

Key: AE = adverse event
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp.

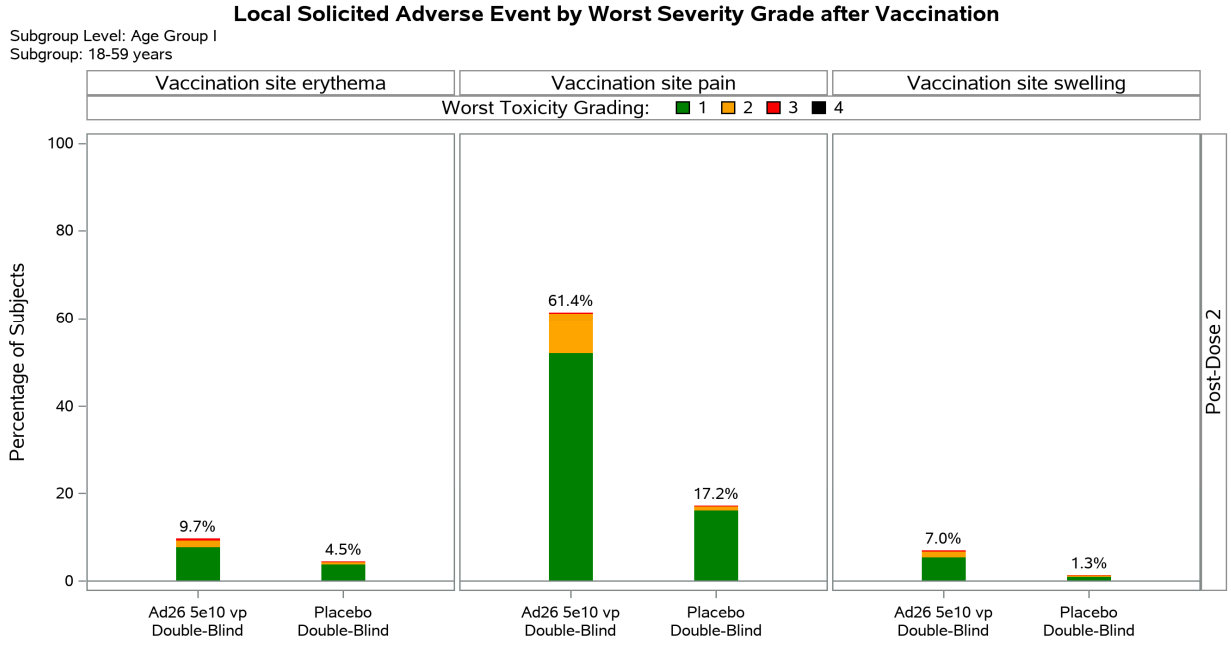
Adapted from: [TSFAESOLLOC02.RTF] [VAC31518\VAC31518COV3009\DBR IA1\RE IA1\PROD\TSFAESOLLOC-SYS02.SAS] 14SEP2021, 23:41

Figure 19: Solicited Local Adverse Events by Worst Severity Grade After Each Vaccination by Age Group; Safety Subset (Study VAC31518COV3009)

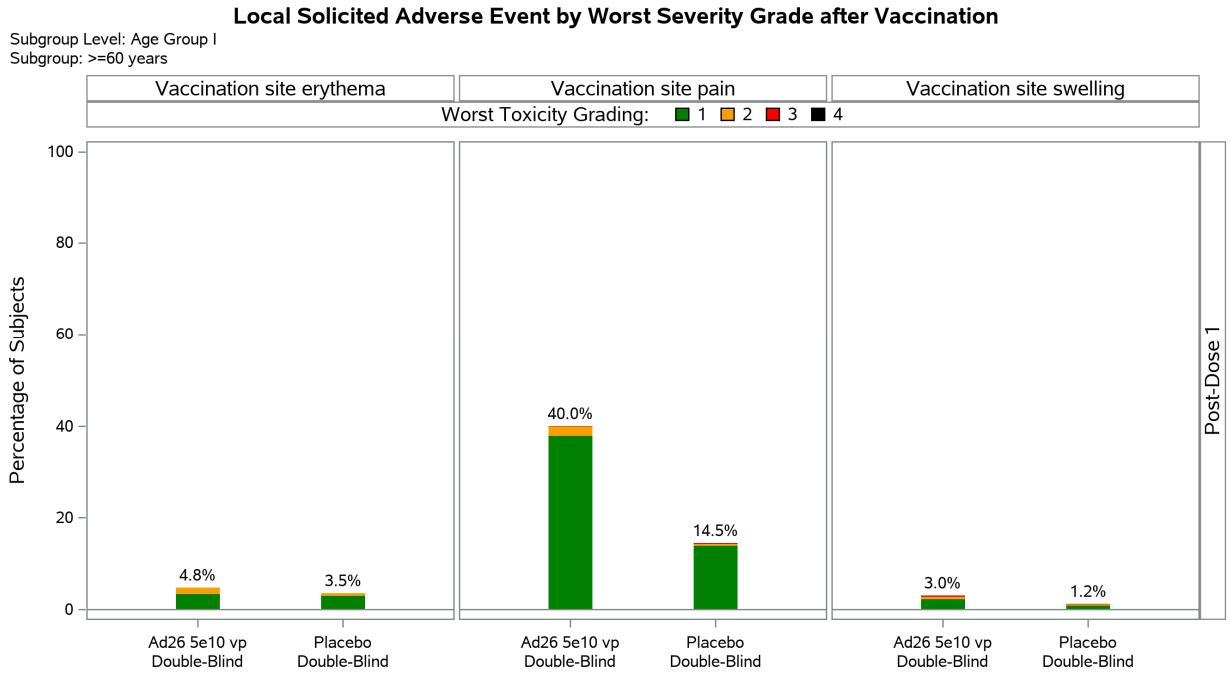
Post-dose 1: 18-59 years of age:



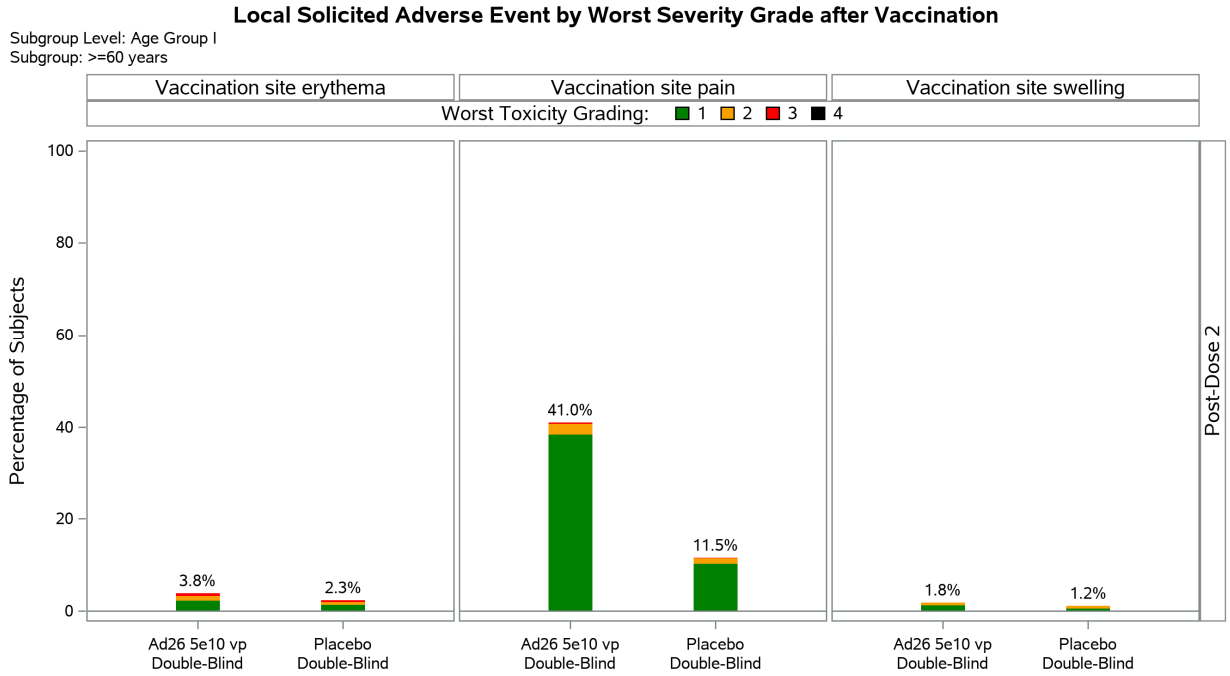
Post-booster: 18-59 years of age:



Post-dose 1: ≥60 years of age:



Post-booster: ≥60 years of age:



Note: Only solicited events occurring in that period are shown. Ad26 5e10 vp: Ad26.COV2.S 5×10^{10} vp

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4.2.2.2.2. Solicited Systemic Adverse Events

The frequency of solicited systemic AEs after each vaccination is presented in Table 11. The frequency of solicited systemic AEs for the younger adult (18-59 years) and older adult (≥60 years) groups is presented in Figure 20. A general trend for lower reactogenicity was observed in older adults.

In the Ad26.COV2.S group, solicited systemic AEs were reported for 58.5% and 52.7% of participants post-dose 1 and post-booster, respectively, with fatigue (44.9% and 41.1%), headache (42.8% and 35.8%), and myalgia (38.9% and 34.7%) being most frequently reported. Most solicited systemic AEs were Grade 1 or Grade 2 in severity. The frequency of Grade 3 events was low and no Grade 4 events were reported. Most solicited systemic AEs were considered to be related to study vaccine. Reactogenicity was transient, with a median duration of 1-2 days after vaccination with Ad26.COV2.S.

Pyrexia of any grade was reported in 5.0% and 2.4% of participants in the Ad26.COV2.S group post-dose 1 and post-booster, respectively. Pyrexia of Grade 3 in severity was reported for 0.1% of Ad26.COV2.S recipients after each dose. The median time to onset of fever after each dose of Ad26.COV2.S was 2 days and the median duration was 1 day.

Table 11: Number of Subjects With Systemic Solicited Adverse Events by Derived Term; Safety Subset (Study VAC31518COV3009)

	Ad26 5e10 vp Double-Blind	Placebo Double-Blind
Analysis set: Safety Subset	3016	3052
Post-dose 1	3015	3052
Subjects with 1 or more Systemic AEs		
Any	1764 (58.5%)	1138 (37.3%)
Grade 3	55 (1.8%)	14 (0.5%)
Fatigue		
Any	1355 (44.9%)	760 (24.9%)
Grade 3	26 (0.9%)	7 (0.2%)
Headache		
Any	1291 (42.8%)	749 (24.5%)
Grade 3	23 (0.8%)	5 (0.2%)
Myalgia		
Any	1172 (38.9%)	468 (15.3%)
Grade 3	23 (0.8%)	4 (0.1%)
Nausea		
Any	546 (18.1%)	316 (10.4%)
Grade 3	9 (0.3%)	5 (0.2%)
Pyrexia		
Any	150 (5.0%)	14 (0.5%)
Grade 3	2 (0.1%)	0
Post-booster	1559	1425
Subjects with 1 or more Systemic AEs		
Any	821 (52.7%)	442 (31.0%)
Grade 3	25 (1.6%)	5 (0.4%)
Fatigue		
Any	641 (41.1%)	293 (20.6%)
Grade 3	14 (0.9%)	2 (0.1%)

Table 11: Number of Subjects With Systemic Solicited Adverse Events by Derived Term; Safety Subset (Study VAC31518COV3009)

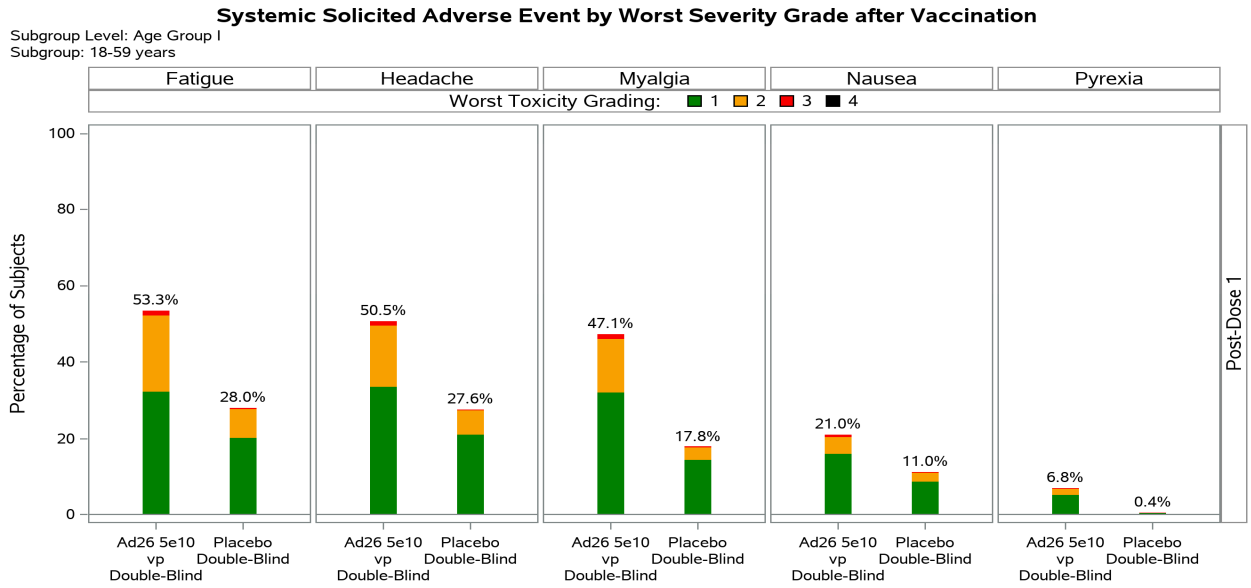
	Ad26 5e10 vp Double-Blind	Placebo Double-Blind
Headache		
Any	558 (35.8%)	270 (18.9%)
Grade 3	10 (0.6%)	3 (0.2%)
Myalgia		
Any	541 (34.7%)	186 (13.1%)
Grade 3	9 (0.6%)	1 (0.1%)
Nausea		
Any	225 (14.4%)	100 (7.0%)
Grade 3	3 (0.2%)	0
Pyrexia		
Any	38 (2.4%)	4 (0.3%)
Grade 3	1 (0.1%)	0

Key: AE = adverse event
Ad26 5e10: Ad26.COV2.S 5×10^{10} vp

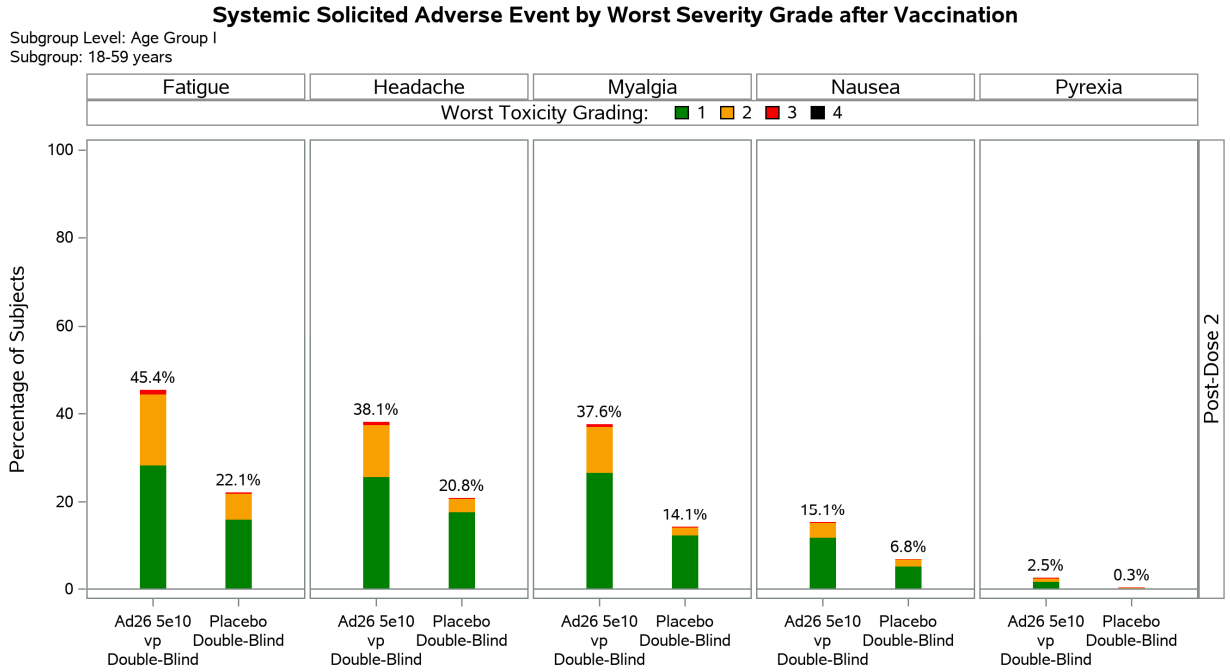
Adapted from: [TSFAESOLSYS02.RTF] [VAC31518\VAC31518COV3009\DBR IA1\RE IA1\PROD\TSFAESOLLOC-SYS02.SAS] 14SEP2021, 23:41

Figure 20: Solicited Systemic Adverse Events by Worst Severity Grade After Each Vaccination by Age Group; Safety Subset (Study VAC31518COV3009)

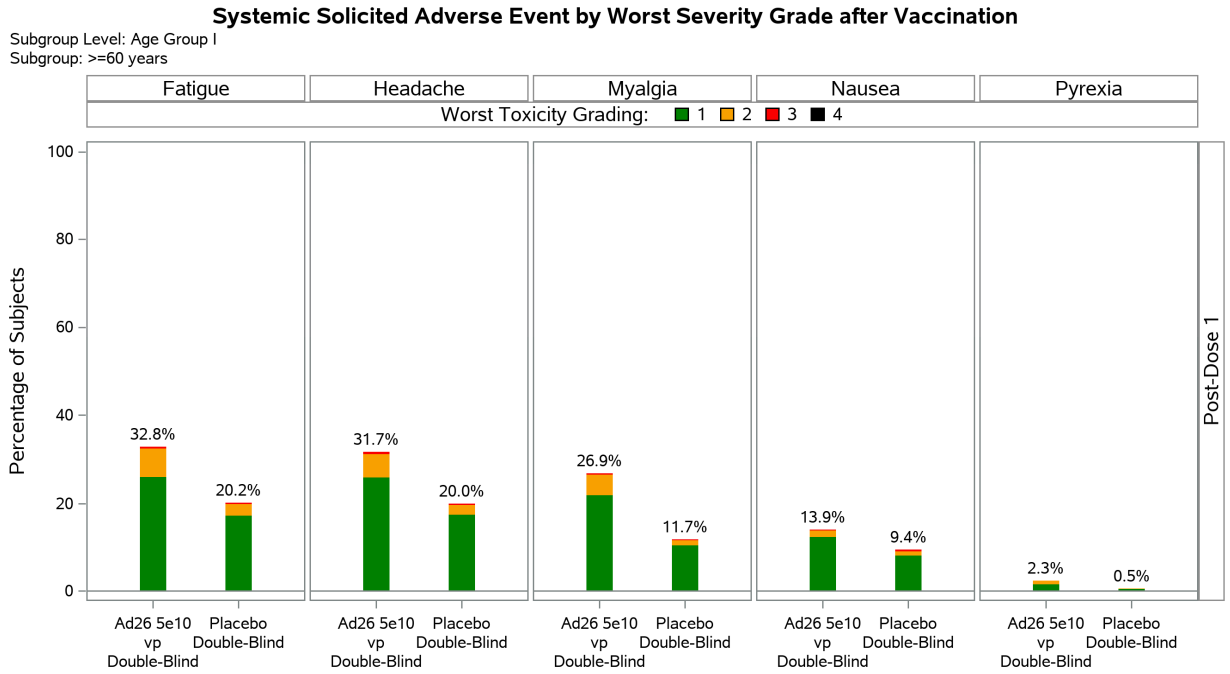
Post-dose 1: 18-59 years of age:



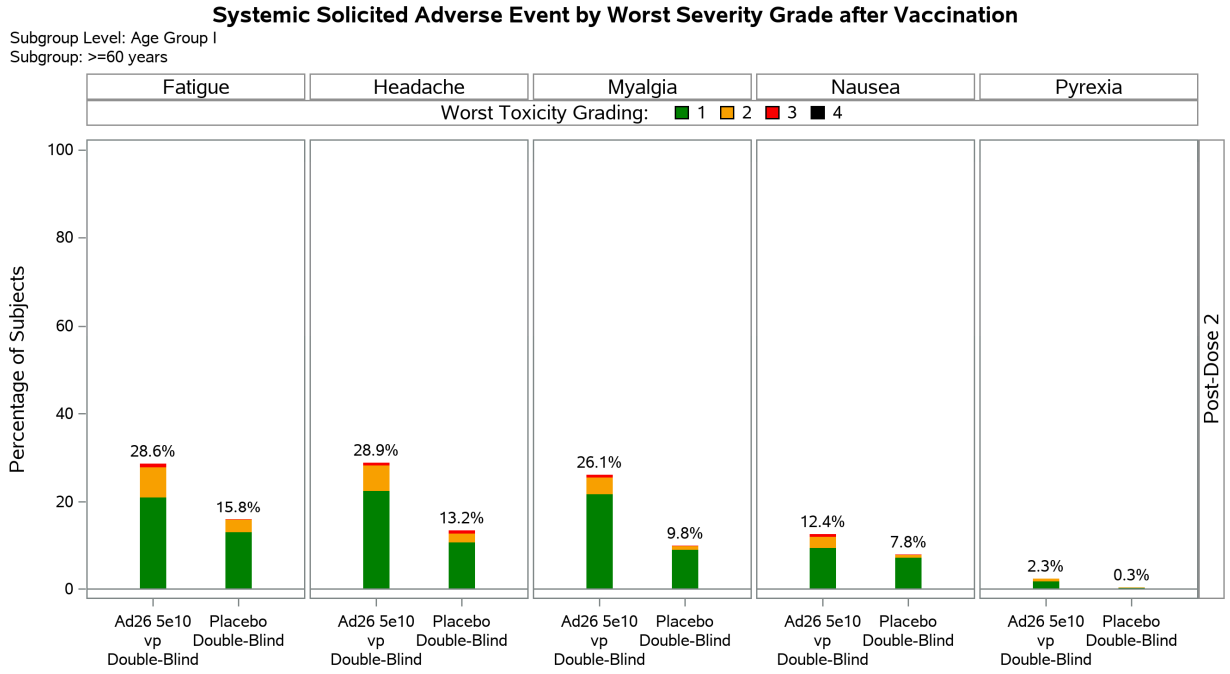
Post-booster: 18-59 years of age:



Post-dose 1: ≥60 years of age:



Post-booster: ≥60 years of age:



Note: Only solicited events occurring in that period are shown. Ad26 5e10 vp: Ad26.COV2.S 5×10^{10} vp

Adapted from: [GSFAESOLSYS03.RTF]
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4.2.2.3. Unsolicited Adverse Events

Overall, unsolicited AEs were reported for 18.6% of participants in the Ad26.COV2.S group and 13.7% of participants in the placebo group.

In the Ad26.COV2.S group, unsolicited AEs were reported for 15.1% and 10.2% of participants post-dose 1 and post-booster, respectively. All unsolicited AEs had a frequency <5% by preferred term. The most frequently reported unsolicited AEs post-booster, which were also recorded as solicited AEs, were headache (2.2%), fatigue (1.9%), and myalgia (1.4%). The most frequently reported unsolicited AEs post-booster that were not recorded as solicited AEs were chills (0.5%), oropharyngeal pain and arthralgia (both 0.4%).

Most unsolicited AEs were Grade 1 or Grade 2 in severity. Unsolicited AEs of at least Grade 3 in severity were reported for 0.7% and 0.8% of participants in the Ad26.COV2.S group post-dose 1 and post-booster, respectively. Post-dose 1, the most frequently reported unsolicited AE of at least Grade 3 in severity was headache (0.3%). Post-booster, nausea (2 participants [0.1%]) was the only unsolicited AE of at least Grade 3 in severity reported for more than 1 participant.

Unsolicited AEs related to vaccination were reported for 9.4% and 5.1% of participants in the Ad26.COV2.S group post-dose 1 and post-booster, respectively, with the most frequently reported being fatigue (2.7% and 1.4%) and headache (2.6% and 1.4%).

4.2.2.4. Immediate Adverse Events

The first 1,000 participants remained under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. No early onset had been observed in either age group at the time of the Day 3 safety review of the initial 1,000 participants; therefore, the observation period at the study site could be reduced to at least 15 minutes for the remaining participants based on local country recommendations.

Solicited and unsolicited immediate AEs were infrequent (<0.5% of participants post-dose 1 or post-booster). Immediate hypersensitivity reactions following vaccination were rare and nonserious. No immediate severe allergic (anaphylaxis) reactions were reported. Anxiety-related reactions to vaccination, including vasovagal reactions such as syncope and presyncope, were rare (<0.1%), and evenly distributed between the Ad26.COV2.S and placebo groups post-dose 1 and post-booster.

4.2.2.5. Deaths

Up to the cutoff date of 25 June 2021, 17 deaths were reported during the double-blind phase: 4 in the Ad26.COV2.S group and 13 in the placebo group. Of the 4 deaths reported in the Ad26.COV2.S group, none had a SARS-CoV-2 positive test during the study. The causes of death by preferred term were lung adenocarcinoma and death of unknown cause after the first dose, and cerebral hemorrhage and myocardial infarction after the booster, all of which were considered not related to vaccination. In the placebo group, 6 of the 13 deaths had a positive SARS-CoV-2 test

during the study, and the causes of death in these participants were COVID-19 or COVID-19 pneumonia.

4.2.2.6. Serious Adverse Events

In the double-blind phase of the study, SAEs were reported for 240 participants in the FAS (104 [0.7%] participants in the Ad26.COV2.S group and 136 [0.9%] participants in the placebo group). The overall frequency of SAEs reported post-dose 1 and post-booster is summarized in Table 12. No increase in the frequency of SAEs was observed post-booster compared with post-dose 1.

Table 12: Number of Subjects with Serious Adverse Events After Each Dose; Full Analysis Set (COV3009)

	Ad26.COV2.S Double-blind	Placebo Double-blind
Double-blind phase	15705	15588
Subjects with 1 or more SAE	104 (0.7%)	136 (0.9%)
Post-dose 1 (Day 1-29)	15705	15588
Subjects with 1 or more SAE	38 (0.2%)	59 (0.4%)
Post-dose 1 FU period (Day 30 to Day 56)	14304	13945
Subjects with 1 or more SAE	38 (0.3%)	52 (0.4%)
Post-booster (Day 57 to Day 85)	8646	8043
Subjects with 1 or more SAE	21 (0.2%)	22 (0.3%)
Post-booster FU period (Day 86 to 6 months post-booster)	5070	4681
Subjects with 1 or more SAE	12 (0.2%)	7 (0.1%)

Key: FU=follow-up; SAE=serious adverse event

A total of 98 (0.6%) participants reported SAEs not associated with COVID-19 in the Ad26.COV2.S group compared with 104 (0.7%) participants in the placebo group. A total of 8 (0.1%) participants reported SAEs associated with COVID-19 in the Ad26.COV2.S group compared with 36 (0.2%) participants in the placebo group.

Related SAEs were reported in 8 participants in the Ad26.COV2.S group and 3 participants in the placebo group. In the Ad26.COV2.S group after the first dose, the related SAEs were pyrexia, pericarditis, allergy to vaccine, and hemoptysis in 1 participant each, and injection site swelling vertigo, and myocardial necrosis marker increased in 1 participant. Related SAEs after the booster dose were facial paresis, pulmonary embolism, and cerebrovascular accident in 1 participant each.

4.2.2.7. Medically-attended Adverse Events

In the double-blind phase of the study, at least 1 MAAE was reported for 1,033 (6.6%) participants in the Ad26.COV2.S group and 1,003 (6.4%) participants in the placebo group. The overall frequency of MAAEs reported post-dose 1 and post-booster is summarized in Table 13. No increase in the frequency of MAAEs was observed post-booster compared with post-dose 1.

Table 13: Number of Subjects with Medically-attended Adverse Events After Each Dose; Full Analysis Set (COV3009)

	Ad26.COV2.S Double-blind	Placebo Double-blind
Double-blind phase	15705	15588
Subjects with 1 or more MAAE	1,033 (6.6%)	1,003 (6.4%)
Post-dose 1 (Day 1-29)	15705	15588
Subjects with 1 or more MAAE	483 (3.1%)	437 (2.8%)
Post-dose 1 FU period (Day 30 to Day 56)	14304	13945
Subjects with 1 or more MAAE	362 (2.5%)	409 (2.9%)
Post-booster (Day 57 to Day 85)	8646	8043
Subjects with 1 or more MAAE	210 (2.4%)	174 (2.2%)
Post-booster FU period (Day 86 to 6 months post-booster)	5070	4681
Subjects with 1 or more MAAE	100 (2.0%)	84 (1.8%)

Key: FU=follow-up; MAAE=medically-attended adverse event

More participants had 1 or more related MAAEs not associated with COVID-19 in the Ad26.COV2.S group (92 [0.6%]) than the placebo group (47 [0.3%]). The most frequently reported related MAAEs not associated with COVID-19 in the Ad26.COV2.S group were headache (10 [0.1%] participants) and fatigue (9 [0.1%] participants).

4.2.2.8. Adverse Events of Special Interest

Following the identification of a safety signal for very rare events of thrombosis with thrombocytopenia syndrome (TTS) in postmarketing data, TTS was considered an AESI in clinical studies. A thrombotic event or thrombocytopenia (defined as platelet count below 150,000/µL [Brighton 2021]) alone was considered a suspected AESI for further investigation.

In the double-blind phase of the COV3009, at least 1 suspected AESI (thrombotic event or thrombocytopenia) was reported for 18 (0.1%) participants in the Ad26.COV2.S group (13 participants after the first dose and 5 participants after the booster) and 22 (0.1%) participants in the placebo group. The majority were thromboembolic events, reported for 14 (0.1%) participants in the Ad26.COV2.S group and 18 (0.1%) participants in the placebo group. Thrombocytopenia was reported as a suspected AESI for 4 (<0.1%) participants in the Ad26.COV2.S group and 5 (<0.1%) participants in the placebo group.

Cases for which a thromboembolic event was reported in combination with thrombocytopenia were adjudicated by an internal AESI adjudication committee. No case in the Ad26.COV2.S group met the Brighton Collaboration criteria Level 1 or CDC criteria Tier 1 (Brighton 2021, Shimabukuro 2021). During the double-blind phase, no cases of thromboembolic events in combination with thrombocytopenia were reported in the Ad26.COV2.S group. Deep vein thrombosis in combination with thrombocytopenia was reported for 1 participant in the Ad26.COV2.S group 100 days post-vaccination. This participant was unblinded before the event

and is therefore counted in the open-label phase. The case was assessed as Brighton Collaboration criteria Level 3 and did not meet CDC Tier 1/ 2 criteria based on available data.

In the placebo group, 1 participant had deep vein thrombosis on Day 27 (double-blind phase) and subsequently pulmonary embolism on Day 29 (open-label phase) in combination with thrombocytopenia; this case was assessed as Brighton Collaboration Level 1 and did not meet CDC Tier 1/ 2 criteria based on available data.

4.2.2.9. Other Adverse Events of Interest

AEs that were deemed to be of interest at time of EUA or for which a notable numerical imbalance was observed in COV3009 are summarized in Table 14 and Table 15. Results from the primary analysis (from the time of EUA application) and/or final analysis of COV3001 are also included. Due to differences in the timing of the conduct of studies COV3001 and COV3009, the duration of follow-up differs.

Convulsions/Seizures

While a numerical imbalance was observed for convulsions/seizures in COV3001 (9 v 4 cases in the final analysis of the double blind phase), in COV3009 no cases were reported in the Ad26.COV2.S group compared with 1 case in the placebo group.

Facial Paralysis

In the double-blind phase of COV3009, no notable numerical imbalance between the Ad26.COV2.S group and placebo group was observed for facial paralysis (3 v 2 cases). Two of the 3 facial paralysis cases in the Ad26.COV2.S group were Bell's palsy, which both occurred after the first dose. The third case was facial paresis, which occurred post-booster.

Tinnitus

A numerical imbalance in cases of tinnitus between the Ad26.COV2.S group and placebo group was observed in the COV3001 primary analysis at the time of the initial EUA application (6 v 0 cases), and tinnitus has been included as an adverse reaction in the US Fact Sheet based on post-authorization data. Of note, while an imbalance of tinnitus cases was also observed in the 28-day period post-dose 1 in COV3009 (4 v 2), no imbalance was observed in the 28-day period post-booster (2 v 2 cases).

Arthritis

In the double-blind phase of COV3009, a numerical imbalance between the Ad26.COV2.S group and placebo group was observed for arthritis (38 v 22 cases in the double-blind phase). Such an imbalance was not seen in COV3001 (4 vs 12 at primary analysis; 40 v 42 at final analysis of the double-blind phase). The observed imbalance in COV3009 was based on events occurring post-dose 1 (24 v 12 cases in the 28-day period post-dose 1); no imbalance was observed in the 28-day period post-booster (4 v 5 cases).

In COV3009, the events reported in the category of arthritis in the Ad26.COV2.S group included arthritis, osteoarthritis, periarthritis, gout, spinal osteoarthritis, gouty arthritis, and oligoarthritis. SAEs in the category of arthritis were reported for 4 participants in the study, all of which were considered not to be related to vaccination. In the Ad26.COV2.S group, SAEs of sub-acromioclavicular osteoarthritis and worsening osteoarthritis were reported for 1 participant each 16 and 50 days, respectively, after the first dose. In the placebo group, 2 participants had SAEs of worsening osteoarthritis. Two non-serious AEs in the category of arthritis were considered related to vaccination: gout flare and oligoarthritis, both of which were reported for participants in the Ad26.COV2.S group.

Hemorrhagic Disorders

In COV3009, hemorrhagic disorders were reported for a low percentage of participants (0.4% and 0.2% in the Ad26.COV2.S group and placebo group, respectively). A numerical imbalance in hemorrhagic disorders was observed between the Ad26.COV2.S group and placebo group (55 v 29 in the double-blind phase, 24 v 14 cases in the 28 days post-dose 1, and 17 v 7 cases in the 28 days post-booster). This imbalance was not observed in COV3001 for the primary analysis (22 v 25) or final analysis (48 v 77) of the double blind phase.

In COV3009, 8 hemorrhagic disorders were SAEs. This included 6 SAEs in the Ad26.COV2.S group: cerebral haemorrhage, worsening of haemorrhagic ovarian cyst, haemothorax, upper gastrointestinal bleed and urethral bleeding, which were considered not related to vaccination, and a related event of hemoptysis. In the placebo group, SAEs of gastrointestinal haemorrhage and lower gastrointestinal bleed were reported, both of which were considered not related to vaccination.

Embolic and Thrombotic Events

Arterial, venous, and unspecified or mixed arterial/venous embolic and thrombotic events are summarized in Table 15.

In the final analysis of the double-blind phase of COV3001, a numerical imbalance was observed between the Ad26.COV2.S group and placebo group for pulmonary embolism (10 v 5) and deep vein thrombosis (11 v 3). Such imbalances were not observed in COV3009 (pulmonary embolism: 1 v 4; deep vein thrombosis 0 v 2). Based on the low incidence of venous thromboembolism in each study, the observed imbalances could be due to chance.

In the double-blind phase of both COV3001 and COV3009, arterial embolic and thrombotic events were reported for fewer participants in the Ad26.COV2.S group than placebo group (COV3001: 9 v 15; COV3009: 6 v 9), which underscores the variability that can be observed with low numbers of events.

Table 14: Number of Subjects with Selected Adverse Events of Interest by Study Period; Full Analysis Set (COV3001 and COV3009)

	COV3001				COV3009							
	Primary Analysis of DB phase (EUA)		Final Analysis of DB phase		Post-dose 1		Post-dose 1 FU		Post-booster		All DB phase	
	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo
N	21895	21888	21894	21882	15705	15588	14304	13946	8646	8043	15705	15588
PYFU	3545	3542	7858	7709	1223	1207	1120	1090	535	500	3343	3216
Tinnitus	6 (<0.1%)	0	15 (0.1%)	4 (<0.1%)	4 (<0.1%)	2 (<0.1%)	4 (<0.1%)	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)	9 (0.1%)	5 (<0.1%)
Convulsions/ seizures	4 (<0.1%)	1 (<0.1%)	9 (<0.1%)	4 (<0.1%)	0	0	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Guillain-Barre syndrome	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0
Facial paralysis	3 (<0.1%)	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	0	3 (<0.1%)	2 (<0.1%)
Pericarditis	1 (<0.1%)	0	1 (<0.1%)	0	1 (<0.1%)	0	0	1 (<0.1%)	0	0	1 (<0.1%)	1 (<0.1%)
Myocarditis	0	0	0	0	0	0	0	1 (<0.1%)		0	0	1 (<0.1%)
Arthritis	4 (<0.1%)	12 (0.1%)	40 (0.2%)	42 (0.2%)	24 (0.2%)	12 (0.1%)	12 (0.1%)	7 (0.1%)	4 (<0.1%)	5 (0.1%)	38 (0.2%)	22 (0.1%)

Key: Ad26 5e10=Ad26.COV2.S at the 5×10^{10} vp dose level, DB=double-blind; EUA= emergency use authorization; FU=follow-up; PYFU=person-year follow-up
COV3009: Post-dose 1=28 days post-dose 1 (Day 1 to Day 29); Post-dose 1 FU=Day 30 to Day 56; Post-booster=28 days post-booster (Day 57 to Day 85)

Table 15: Number of Subjects with Embolic and Thrombotic Events; Full Analysis Set (COV3001 and COV3009)

	COV3001				COV3009							
	Final Analysis DB phase		Post-dose 1		Post-dose 1		Post-dose 1 FU		Post-booster		All DB phase	
	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo
N	**21894**	**21882**	**21894**	**21882**	**15705**	**15588**	**14304**	**13946**	**8646**	**8043**	**15705**	**15588**
Person-year follow-up	7858	7709	1673	1670	1223	1207	1120	1090	535	500	3343	3216
Embolic and thrombotic events (SMQ) Any	40 (0.2%)	36 (0.2%)	14 (0.1%)	10 (<0.1%)	2 (<0.1%)	6 (<0.1%)	7 (<0.1%)	9 (0.1%)	3 (<0.1%)	3 (<0.1%)	14 (0.1%)	18 (0.1%)
EMBOLIC AND THROMBOTIC EVENTS, ARTERIAL (sub_SMQ1)												
Any	9 (<0.1%)	15 (0.1%)	3 (<0.1%)	3 (<0.1%)	1 (<0.1%)	4 (<0.1%)	4 (<0.1%)	3 (<0.1%)	0	2 (<0.1%)	6 (<0.1%)	9 (0.1%)
Acute myocardial infarction	2 (<0.1%)	7 (<0.1%)	0	2 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)			2 (<0.1%)	1 (<0.1%)
Myocardial infarction	2 (<0.1%)	3 (<0.1%)	1 (<0.1%)	0	0	2 (<0.1%)			0	2 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Transient ischaemic attack	2 (<0.1%)	3 (<0.1%)			0	2 (<0.1%)	1 (<0.1%)	0			1 (<0.1%)	2 (<0.1%)
Carotid artery occlusion	0	1 (<0.1%)	0	1 (<0.1%)								
Peripheral artery occlusion	0	1 (<0.1%)					0	1 (<0.1%)			0	1 (<0.1%)
Blindness transient	1 (<0.1%)	0	1 (<0.1%)	0								
Ischaemic stroke	3 (<0.1%)	0	1 (<0.1%)	0			2 (<0.1%)	1 (<0.1%)			2 (<0.1%)	1 (<0.1%)
EMBOLIC AND THROMBOTIC EVENTS, VESSEL TYPE UNSPECIFIED AND MIXED ARTERIAL AND VENOUS (sub_SMQ1)												
Any	7 (<0.1%)	13 (0.1%)	3 (<0.1%)	3 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)	3 (<0.1%)	2 (<0.1%)	0	6 (<0.1%)	3 (<0.1%)
Cerebrovascular accident	4 (<0.1%)	6 (<0.1%)					1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)	1 (<0.1%)
Cerebral infarction	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)			0	1 (<0.1%)			0	1 (<0.1%)
Hemiparesis	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)			0	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Embolism	0	1 (<0.1%)			1 (<0.1%)	0					1 (<0.1%)	0
Haemorrhoids thrombosed	0	1 (<0.1%)	0	1 (<0.1%)								
Hemiplegia	1 (<0.1%)	1 (<0.1%)										
Paraparesis	0	1 (<0.1%)										
Vascular stent occlusion	0	1 (<0.1%)										
Brain stem stroke	1 (<0.1%)	0	1 (<0.1%)	0								
Monoplegia							1 (<0.1%)	0			1 (<0.1%)	0
Cerebral thrombosis							0	1 (<0.1%)			0	1 (<0.1%)
EMBOLIC AND THROMBOTIC EVENTS, VENOUS (sub_SMQ1)												
Any	25 (0.1%)	9 (<0.1%)	8 (<0.1%)	4 (<0.1%)	0	2 (<0.1%)	1 (<0.1%)	3 (<0.1%)	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)	6 (<0.1%)
Pulmonary embolism	10 (<0.1%)	5 (<0.1%)	2 (<0.1%)	2 (<0.1%)	0	1 (<0.1%)	0	3 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	4 (<0.1%)
Deep vein thrombosis	11 (0.1%)	3 (<0.1%)	4 (<0.1%)	2 (<0.1%)	0	1 (<0.1%)			0	1 (<0.1%)	0	2 (<0.1%)
CVST*	0	1 (<0.1%)										
Thrombophlebitis	0	1 (<0.1%)										
Embolism venous	1 (<0.1%)	0										
Retinal vein thrombosis	1 (<0.1%)	0										
Thrombophleb. superfic.	1 (<0.1%)	0					1 (<0.1%)	0			1 (<0.1%)	0
Transverse sinus thromb.	1 (<0.1%)	0	1 (<0.1%)	0								

	COV3001				COV3009							
	Final Analysis DB phase		Post-dose 1		Post-dose 1		Post-dose 1 FU		Post-booster		All DB phase	
	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo	Ad26 5e10	Placebo
Venous thrombosis limb	1 (<0.1%)	0	1 (<0.1%)	0								

Key: Ad26 5e10=Ad26.COV2.S at the 5×10^{10} vp dose level, CVST=Cerebral venous sinus thrombosis, DB=double-blind, SMQ=Standardized MedDRA (Medical dictionary for regulatory activities) query

Post-dose 1=28 days post-dose 1 (Day 1 to Day 29); Post-dose 1 FU=Day 30 to Day 56; Post-booster=28 days post-booster (Day 57 to Day 85)

4.2.3. Overview of Safety in Other Clinical Studies with an Ad26.COV2.S Booster

In addition to COV3009, Ad26.COV2.S at the 5×10^{10} vp dose level has been administered as a booster in Phase 1-2 studies (Table 9). Safety and reactogenicity results from study COV1001 Cohort 2a (6-month booster) and study COV2008 (≥6 month booster; dose-level blinded data) are described in Section 4.2.3.1 and Section 4.2.3.2, respectively.

4.2.3.1. COV1001 Cohort 2a

In the Phase 1/2a study COV1001, participants (aged ≥18 to ≤55 years) in Cohort 2a Group 2 (6-month booster group) received Ad26.COV2.S at the 5×10^{10} vp dose level as a primary dose and a booster with a 6-month interval (6-month booster group). Of the 29 participants in this group, 19 participants received the booster.

The frequency of solicited local AEs and solicited systemic AEs after each vaccination is presented in Table 16 and Table 17, respectively.

In the 6-month booster group, solicited local AEs were reported for 82.8% and 78.9% of participants post-dose 1 and post-booster, respectively. All solicited local AEs were Grade 1 or 2 in severity.

Solicited systemic AEs were reported for 79.3% and 57.9% of participants in the booster group post-dose 1 and post-booster, respectively. Pyrexia was reported for 10.3% of participants post-dose 1 and no participants post-booster. One Grade 3 AE of headache was reported post-dose 1; all solicited systemic AEs were Grade 1 or 2 in severity post-booster.

The frequency of unsolicited AEs was 17.2% post-dose 1 and 10.5% post-booster, and all were Grade 1 or 2 in severity.

Up to the cut-off date of 21 July 2021, no deaths were reported in the booster group. None of the participants experienced an SAE considered related to the study vaccine post-dose 1 or post-booster.

Table 16: Number of Subjects with Local Solicited Adverse Events by Derived Term; Cohort 2A; Full Analysis Set (Study VAC31518COV1001)

	Ad26 5e10, B: Ad26 5e10	Ad26 5e10, B: PL	Placebo, B: PL
Analysis set: Full	29	90	17
Post-Dose 1	29	90	17
Subjects with 1 or more Local AEs	24 (82.8%)	67 (74.4%)	4 (23.5%)
Vaccination site erythema	1 (3.4%)	2 (2.2%)	0
Vaccination site pain	23 (79.3%)	67 (74.4%)	4 (23.5%)
Vaccination site swelling	1 (3.4%)	1 (1.1%)	0
Post-Booster	19	62	1
Subjects with 1 or more AEs	15 (78.9%)	9 (14.5%)	0
Vaccination site erythema	0	0	0
Vaccination site pain	15 (78.9%)	9 (14.5%)	0
Vaccination site swelling	0	0	0

Key: AE = adverse event, B = booster, PL = placebo
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp.
All subject data up to July 21, 2021 are included

Adapted from: [tsfaesolloc02-c2a.rtf] [Events/ae/pgm/ae03.sas] 06SEP2021, 8:59:19AM SAS 9.4

Table 17: Number of Subjects With Systemic Solicited Adverse Events by Derived Term; Cohort 2A; Full Analysis Set (Study VAC31518COV1001)

	Ad26 5e10, B: Ad26 5e10	Ad26 5e10, B: PL	Placebo, B: PL
Analysis set: Full	29	90	17
Post-Dose 1	29	90	17
Subjects with 1 or more Systemic AEs			
Any	23 (79.3%)	68 (75.6%)	8 (47.1%)
Grade 3	1 (3.4%)	11 (12.2%)	1 (5.9%)
Derived Term			
Fatigue			
Any	17 (58.6%)	52 (57.8%)	7 (41.2%)
Grade 3	0	5 (5.6%)	1 (5.9%)
Headache			
Any	16 (55.2%)	46 (51.1%)	4 (23.5%)
Grade 3	1 (3.4%)	3 (3.3%)	0
Myalgia			
Any	17 (58.6%)	47 (52.2%)	4 (23.5%)
Grade 3	0	1 (1.1%)	0
Nausea			
Any	8 (27.6%)	23 (25.6%)	2 (11.8%)
Grade 3	0	3 (3.3%)	0

Table 17: Number of Subjects With Systemic Solicited Adverse Events by Derived Term; Cohort 2A; Full Analysis Set (Study VAC31518COV1001)

	Ad26 5e10, B: Ad26 5e10	Ad26 5e10, B: PL	Placebo, B: PL
Pyrexia			
Any	3 (10.3%)	19 (21.1%)	0
Grade 3	0	5 (5.6%)	0
Post-Booster	19	62	1
Subjects with 1 or more Systemic AEs			
Any	11 (57.9%)	19 (30.6%)	0
Grade 3	0	1 (1.6%)	0
Derived Term			
Fatigue			
Any	5 (26.3%)	13 (21.0%)	0
Grade 3	0	1 (1.6%)	0
Headache			
Any	9 (47.4%)	13 (21.0%)	0
Grade 3	0	0	0
Myalgia			
Any	4 (21.1%)	7 (11.3%)	0
Grade 3	0	0	0
Nausea			
Any	2 (10.5%)	3 (4.8%)	0
Grade 3	0	1 (1.6%)	0
Pyrexia			
Any	0	0	0

Key: AE = adverse event, B = booster, PL = placebo
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp.
All subject data up to July 21, 2021 are included

Adapted from: [tsfaesolsys02-c2a.rtf] [Events/ae/pgm/ae03.sas] 06SEP2021, 8:59:31AM SAS 9.4

4.2.3.2. COV2008

Study COV2008 is an ongoing, randomized, double-blind, Phase 2 study to evaluate the immunogenicity, reactogenicity and safety of Ad26.COV2.S (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) administered as booster vaccination in adults ≥18 years of age ≥6 months after receiving a primary vaccination with Ad26.COV2.S (1-dose at 5×10^{10} vp in study COV3001) or Pfizer's BNT162b2 (2-dose). The study is planned to include approximately 1,540 participants.

Preliminary dose level-blinded safety data are available for 370 participants who received an Ad26.COV2.S booster following Ad26.COV2.S primary vaccination. Data entry and collection were still ongoing at the time of the data extraction for this study (7 September 2021); therefore, these data represent an incomplete snapshot.

Randomization to a booster group (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) was based on a 3:3:1 ratio. Therefore, of the 370 participants for whom dose-level blinded data were available at the date of data extraction, an estimated 159 participants received a 5×10^{10} vp booster.

Dose level-blinded 7-day reactogenicity data were available for 244 participants (estimated 105 participants who received a 5×10^{10} vp booster). For these participants, almost all solicited AEs were Grade 1 in severity; one Grade 3 solicited AE was reported (Table 18). The most frequently reported solicited local AE was vaccination site pain. The most frequently reported solicited systemic AEs were fatigue, headache, and myalgia (Table 19).

At the time of the data extraction, not all 370 participants had completed the 28-day post-vaccination reporting period for unsolicited AEs. Of the unsolicited AEs reported, almost all were Grade 1 in severity, none were Grade 3 or 4. No SAEs were reported.

Table 18: Number of Subjects With Local Solicited Adverse Events by Derived Term; Cohort 1; Full Analysis Set (Study VAC31518COV2008)

	All Subjects
Analysis set: Full	370
Post-vaccination in study COV2008	244
Subjects with 1 or more Local AEs	
Any	125 (51.2%)
Grade 3	1 (0.4%)
Vaccination Site Erythema	
Any	7 (2.9%)
Grade 3	1 (0.4%)
Vaccination Site Pain	
Any	122 (50.0%)
Grade 3	0
Vaccination Site Swelling	
Any	8 (3.3%)
Grade 3	1 (0.4%)

Key: AE = adverse event

Adapted from [TSFAESOLLOC02-C1.RTF] [VAC31518\VAC31518COV2008\DBR EUA AMENDMENT SEP2021\RE EUA AMENDMENT SEP2021\PROD\TSFAESOLLOC-SYS02.SAS] 09SEP2021, 12:11

Table 19: Number of Subjects With Systemic Solicited Adverse Events by Derived Term; Cohort 1; Full Analysis Set (Study VAC31518COV2008)

	All Subjects
Analysis set: Full	370
Post-vaccination in study COV2008	244
Subjects with 1 or more Systemic AEs	115 (47.1%)
Fatigue	88 (36.1%)
Headache	64 (26.2%)
Myalgia	62 (25.4%)
Nausea	19 (7.8%)
Pyrexia	2 (0.8%)

Key: AE = adverse event
Note: All systemic AEs were Grade 1 or 2 in severity

Adapted from [TSFAESOLSYS02-C1.RTF]
[VAC31518\VAC31518COV2008\DBR EUA AMENDMENT SEP2021\RE EUA AMENDMENT SEP2021\PROD\TSFAESOLLOC-SYS02.SAS] 09SEP2021, 12:11

4.3. Conclusions

The acceptable safety and reactogenicity profile of a single-dose Ad26.COV2.S regimen has been established from clinical studies and postmarketing experience. An estimated 33.5 million doses of Ad26.COV2.S have been administered worldwide through 31 August 2021.

A total of 9,379 participants ≥18 years of age, including 2,383 participants ≥60 years of age have received 2 doses of Ad26.COV2.S 5×10^{10} vp in clinical studies, with the booster administered after an interval of 2 months to ≥6 months. Overall, Ad26.COV2.S has an acceptable reactogenicity profile after both the first dose and booster. The reactogenicity post-booster is similar or milder than post-dose 1.

In study COV3009, 8,655 participants received a second dose of Ad26.COV2.S 5×10^{10} vp. No increase in reactogenicity was observed post-booster compared with post-dose 1, with similar overall frequencies of solicited local and systemic AEs.

Numerical imbalances that were observed in COV3001 for the AEs of interest pulmonary embolism, deep vein thrombosis, and convulsions/seizures were not observed in COV3009. A numerical imbalance between the Ad26.COV2.S group and placebo group for hemorrhagic disorders was observed in COV3009 (55 v 29 in the double-blind phase), but this was not observed in COV3001 (48 v 77 in double-blind phase). In COV3009, numerical imbalances were also observed for arthritis (38 v 22) and tinnitus (9 v 5). An imbalance for arthritis was not observed in the double-blind phase of COV3001 (40 v 42). In COV3009, the imbalance for arthritis between the Ad26.COV2.S group and placebo group was observed in the 28-day period post-dose 1 (24 v 12) but not post-booster (4 v 5). Similarly for tinnitus, the imbalance in COV3009 was observed in the 28-day period post-dose 1 (4 v 2) but not post-booster (2 v 2).

Overall, no new safety concerns have been identified after an Ad26.COV2.S booster.

5. PHARMACOVIGILANCE/SAFETY MONITORING PLAN

Janssen has drafted a comprehensive pharmacovigilance plan to identify safety concerns and procedures for collecting and evaluating ongoing clinical safety data relevant to the use of Ad26.COV2.S. Upon authorization, Janssen will include the booster dose into the ongoing pharmacovigilance activities previously agreed with the FDA for the single-dose regimen.

5.1. Routine Pharmacovigilance

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

- **Safety reporting.** Spontaneous and solicited reports, including all SAEs (regardless of attribution to vaccination) and Multisystem Inflammatory Syndrome will be submitted to Vaccine Adverse Event Reporting System (VAERS) within 15 calendar days.
- **Active follow-up.** Active follow-up will continue to be performed for all SAEs, among individuals who receive Ad26.COV2.S under the EUA; this will include 2 phone call attempts to the reporter or healthcare provider.
- **Standard/passive follow-up.** Individual Case Safety Reports (ICSRs) 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 with Health Care Providers. Additionally, questions related to the adverse event of special interest (AESI) list are included in the standard vaccine AE follow-up questionnaire on a case-by-case basis. Targeted follow-up questionnaires are used to collect follow-up information on reports of Hypersensitivity/Anaphylaxis, COVID-19 vaccine failure, and Venous thromboembolism.
- **Periodic aggregate review of safety data.** Following FDA guidance, Janssen will continue to submit regular safety summary reports containing a review of safety information received during the reporting interval, as well as ad hoc cumulative data as appropriate.
- **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, postmarketing data, and all other sources of information is reviewed on a regular basis. Routine aggregate signal detection includes regular surveillance of AE reports received in Janssen's Global Safety Database. Additional reviews are performed in external databases: VAERS, WHO VigiBase and EudraVigilance.

5.2. Additional PV Activities

Additional PV activities for data collection from both ongoing and planned interventional clinical studies and active surveillance studies are listed below (see Appendix 1 for the study designs):

Interventional Studies

Ongoing and planned interventional studies evaluate the safety of multiple dose regimens:

- COV3001 and COV3009 long-term safety data: In both studies, participants who initially received placebo were offered a single dose of Ad26.COV2.S vaccine. All participants who received a single dose of Ad26.COV2.S are planned to be offered an Ad26.COV2.S booster. Long-term safety follow-up post-booster will continue for 1 year in COV3001 and at least 6 months in COV3009.
- COV2001: A randomized, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate two dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive.
- COV3005 - A coadministration study of Ad26.COV2.S with seasonal influenza vaccine; participants will have previously received primary vaccination with an authorized/licensed COVID-19 vaccine (completed ≥6 months prior to first study vaccination) or be COVID-19 vaccine-naïve.
- Study to evaluate use in immunocompromised participants.
- 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 1- or 2-dose regimen in healthy children from 12 to 17 years inclusive.
- COV2004 – Assessment of the safety and immunogenicity of Ad26.COV2.S in pregnant women and their offspring.
- COV2008 – A randomized, double-blind, Phase 2 study to evaluate the immunogenicity, reactogenicity and safety of Ad26.COV2.S (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) administered as booster vaccination in adults ≥18 years of age ≥6 months after receiving a primary vaccination with Ad26.COV2.S (1-dose in study COV3001) or Pfizer's BNT162b2 (2-dose).

Non-Interventional Studies

- COV4001 - 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.

- COV4002 - An observational post-authorization study to assess the effectiveness of Ad26.COV2.S for prevention of COVID-19 using real-world data from US health insurance claims databases. The goals of this study are to assess the real-world effectiveness of Ad26.COV2.S to prevent observed COVID-19 in US individuals vaccinated according to the national immunization recommendations.
- COV4005 - 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.
- COV4003 - 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.
- COV4004 - 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.

Where applicable, COV4001-4005 study protocols will be amended to assess the safety and effectiveness of a booster dose of Ad26.COV2.S.

6. BENEFIT-RISK ASSESSMENT

The final analysis of COV3001 demonstrate that the single dose Ad26.COV2.S primary regimen provides substantial protection against severe COVID-19 disease, hospitalization and death and maintains a favorable benefit-risk profile. Durable protection against observed COVID-19 and COVID-19 related hospitalizations was confirmed by large real-world-effectiveness studies in the US and South Africa, including in calendar time that the Delta variant was highly prevalent. Therefore, the single dose Ad26.COV2.S regimen continues to be an important tool in the fight against COVID-19.

In addition, the efficacy and safety data presented in this briefing document support a favorable benefit-risk profile for Ad26.COV2.S when given as a booster dose after the single dose primary regimen in adults ≥18 years of age.

A booster dose is recommended at 6 months or later, based on the strength of the immune responses, although a booster dose may be administered as early as 2 months. The need for a booster dose and/or its timing will depend on the local/epidemiological situation and the needs of individuals/specific populations.

In the early stages of a pandemic, a single dose vaccine is an efficient tool to rapidly increase vaccine uptake and reduce the burden on health care systems by preventing severe disease outcomes, especially where supply limitations were present. In the current stage of the pandemic, and given emergence of different variants under certain circumstances, focus may shift to protecting individuals by maximizing and prolonging vaccine-induced protection, not only against severe/critical COVID-19, but also against symptomatic infection, to potentially reduce transmission, and raise immunity to increase the probability of protection against future variants of concern. This is important in the US, where the low vaccination coverage puts even vaccinated people at risk because of strong circulation of the highly transmissible delta variant. A booster dose of the Janssen COVID-19 vaccine was shown to safely increase protection against all forms of COVID-19 and should therefore be considered for optimal individual protection.

6.1. Rationale for the Ad26.COV2.S Booster Dose

A single dose of Ad26.COV2.S elicited a durable humoral and cellular immune responses up to at least 6 to 8 months post vaccination and durable protection against severe/critical COVID-19 (including hospitalizations and deaths related to COVID-19) up to at least 6 months post vaccination in adults ≥18 years of age. In COV3001, no waning of protection against moderate to severe/critical COVID-19 was observed in the US over the observation period. However, a decrease in protection over time against moderate to severe/critical COVID-19 globally was observed which was driven by reduced efficacy against some of the emerging SARS-CoV-2 variants in regions outside the US. A single dose of Ad26.COV2S elicited a neutralizing antibody response against SARS-CoV-2 VOC but the response was lower compared to the reference strain.

Based on recent data, administration of a booster dose resulted in increased protection against symptomatic COVID-19, increased strength and breadth of immune responses against variants and increase protection against severe/critical COVID-19.

6.2. Efficacy of the Ad26.COV2.S Booster Dose

An Ad26.COV2.S booster dose administered 2 months after the primary Ad26.COV2.S dose substantially increases protection, especially against symptomatic COVID-19 (see Table 20 and see Figure 21), including when caused by SARS-CoV-2 variants of concern (see Figure 22).

The primary analysis results of Janssen's 2-dose efficacy study COV3009 includes data from 7484 participants who received 2 doses of Ad26.COV2.S and 7008 participants who received 2 doses of placebo in the PP set. Median follow-up time after the second dose in the double-blind phase was 36 days (0-172 days), with 29.3% of participants in the per protocol set with at least 2 months of follow-up after the 2nd dose. Sequencing data were available from 68.0% of cases in the double-blind phase of the study. The reference sequence was only present in 6.0% of the sequenced strains overall and 22.9% in the US.

In the US, where the dominant strain during the double-blind phase of COV3001 (single dose regimen) was the reference strain, VE was stable when comparing the COV3001 primary and final

analysis. After the Ad26.COV2.S booster dose (COV3009), VE against symptomatic COVID-19[3] was 94% in the US.

Table 20: VE After Ad26.COV2.S Booster Dose 2 Months after First Dose (COV3009) and After Single Ad26.COV2.S Dose (COV3001)

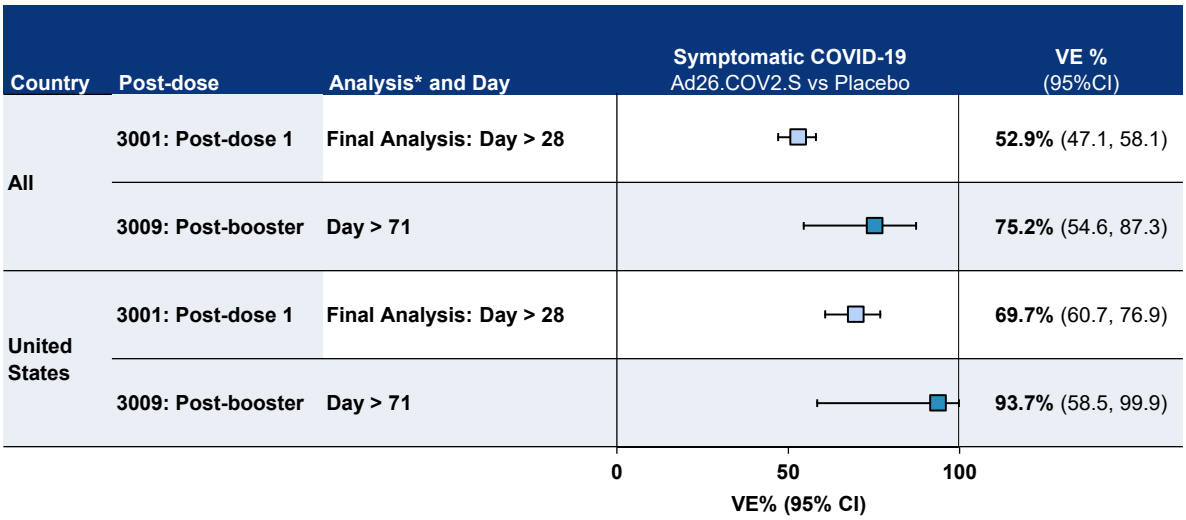
	COV3009 primary analysis, VE 14 days after Ad26.COV2.S booster dose	**COV3001 final analysis double-blind phase, VE 28 days after single Ad26.COV2.S dose**
Symptomatic COVID-19*		
US	94% (95% CI 59;100)	70% (95% CI 61;77)
Global	75% (95% CI 55;87)	53% (95% CI 47,58)
Severe/Critical COVID-19		
Global	100% (adjusted 95% CI 33 100.00)	75% (adjusted 95% CI 65;82)

* moderate to severe/critical COVID-19 per the case definitions in Appendix 2.

The number of cases in COV3009 that were infected with the Alpha or Mu variant were sufficient to allow a variant specific analysis of vaccine efficacy, which demonstrated that a homologous booster of Ad26.COV2.S increases protection against symptomatic infection for different variants. (see Figure 22). At the analysis cut-off date in June 2021, the Delta variant was not yet prominent in our study population, so vaccine efficacy for this variant are not available.

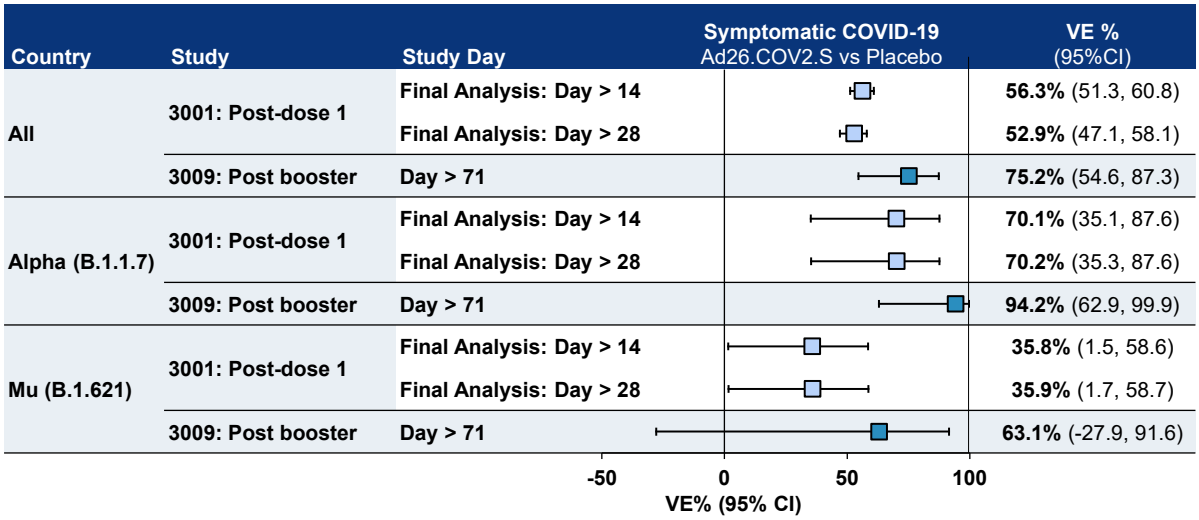
[3] Note that COVID-19 severity case definitions are provided in Appendix 2. Throughout this document, the term 'symptomatic COVID-19' is used to indicate mild, moderate and severe/critical COVID-19 according to these definitions. The primary case definition of moderate to severe/critical COVID-19 was so comprehensive that a very few cases were found to be outside of this definition and considered mild. Therefore, the terms moderate to severe/critical COVID-19 and symptomatic COVID-19 are used interchangeably.

Figure 21: VE Against Symptomatic COVID-19: Single Dose (COV3001) vs Booster Dose 2 Months After First Dose (COV3009)



*COV3001 primary analysis cut-off data: January 2021; COV3001 final analysis cut-off date: July 2021 (of note: in this analysis, the last available onset primary endpoint for US was in April 2021); COV3009 primary analysis cut-off date: June 2021.

Figure 22: VE Against Symptomatic COVID-19 by Variant: Single Dose (COV3001) vs Booster Dose 2 Months After First Dose (COV3009)



*COV3001 primary analysis cut-off data: January 2021; COV3001 final analysis cut-off date: July 2021 (of note: in this analysis, the last available onset primary endpoint for US was in April 2021); COV3009 primary analysis cut-off date: June 2021.

6.3. Immunogenicity of the Ad26.COV2.S Booster Dose

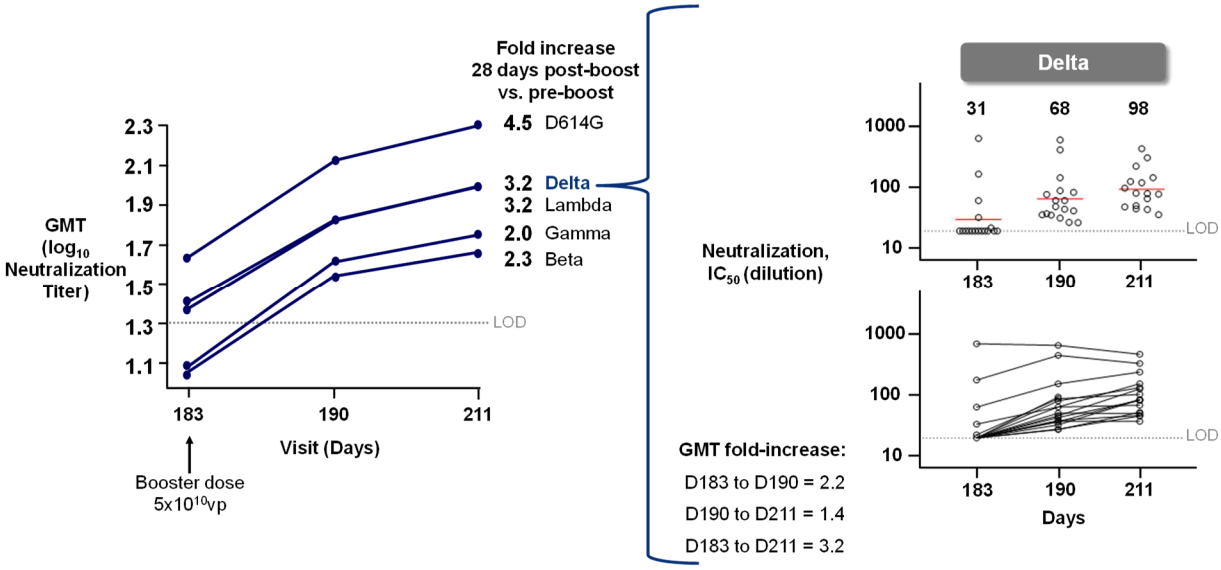
The immunogenicity of an Ad26.COV2.S booster dose was measured over different time intervals throughout the different AD26.COV2.S clinical studies. Overall, the data show that an Ad26.COV2.S booster dose administered 2 to 6 or more months after the primary regimen increases immunogenicity versus the 1-dose regimen and induces a strong and broad immune

response that is expected to confer extended durable protection against COVID-19, including variants of concern.

A post-hoc NI analysis was performed on 17 participants from COV1001 who received a booster dose 6 months after the first dose. While the study did not include a pre-specified non-inferiority objective, the fold increase in the ELISA assay and the psVNA assay from 28 days post dose 1 to 7 days post booster dose (Day 190) and from 28 days post dose 1 to 28 days post booster dose (Day 211) have met the standard NI criteria.

Using an internally developed 'fit for purpose' pseudovirus neutralization assay specific for the variants of concern, a substantial increase in variant-specific neutralizing antibodies was observed, including the Delta variant (see Figure 23). By 28 days post boost, all 17 participants evaluated had detectable neutralizing antibodies against the Delta variant.

Figure 23: SARS-CoV-2 [S] Variant psVNA GMT: Booster Dose $5x10^{10}$ vp 6 Months After First Dose (COV1001 Cohort 2a)



A larger interval between the primary vaccination with Ad26.COV2.S and a homologous booster dose resulted in a larger increase in humoral immune responses (ELISA titers) versus the 1-dose regimen (see Figure 24), for both participants 18-55 years of age and ≥65 years of age, going from a 4-6 fold increase (both age groups) with a 2-month boost to a 12-fold increase with a 6-month boost (younger age group only).

Figure 24: Spike Binding Antibody Levels: Booster Dose 2-3 Months (COV2001) vs 6 Months (COV1001) After First Dose

		Spike Binding Antibodies				
		Boost 2 Months after Primary Dose*		Boost 3 Months after Primary Dose*		Boost 6 Months after Primary Dose**
		18-55 years (N=52)	≥ 65 years (N=29)	18-55 years (N=27)	≥ 65 years (N=20)	18-55 years (N=20)
Pre-Boost*	**GMC (% resp.)**	497 (96%)	318 (97%)	456 (96%)	378 (100%)	798 (100%)
28 Days Post Boost	**GMC (% resp.)**	1638 (100%)	1688 (100%)	2017 (100%)	3233 (100%)	5108 (100%)
28 Days Post Boost vs 29 Days Post Dose 1	**Fold-increase**	**4.6**	**6.1**	**5.6**	**9.9**	**12**

* Data from COV2001 Group 1
Data from COV1001 Cohort 2a

6.4. Safety of Booster Vaccination

A total of 9,379 participants ≥18 years of age, including 2,383 participants ≥60 years of age, have received 2 doses of Ad26.COV2.S 5×10^{10} vp in clinical studies, with the booster administered after an interval of 2 months to ≥6 months. Overall, Ad26.COV2.S has an acceptable reactogenicity profile after both the first dose and booster, with the reactogenicity post-booster being similar or milder than post-dose 1.

Numerical imbalances that were observed in COV3001 for the AEs of interest pulmonary embolism, deep vein thrombosis, and convulsions/seizures were not observed in COV3009. A numerical imbalance between the Ad26.COV2.S group and placebo group for hemorrhagic disorders was observed in COV3009 (55 v 29 in the double-blind phase), but this was not observed in COV3001 (48 v 77 in double-blind phase). In COV3009, numerical imbalances were also observed for arthritis (38 v 22) and tinnitus (9 v 5). An imbalance for arthritis was not observed in the double-blind phase of COV3001 (40 v 42). In COV3009, the imbalance for arthritis between the Ad26.COV2.S group and placebo group was observed in the 28-day period post-dose 1 (24 v 12) but not post-booster (4 v 5). Similarly for tinnitus, the imbalance in COV3009 was observed in the 28-day period post-dose 1 (4 v 2) but not post-booster (2 v 2).

Overall, no new safety concerns have been identified after an Ad26.COV2.S booster.

Very rare cases of TTS have also been reported following vaccination with the Astra Zeneca COVID-19 vaccine AZD1222, which uses a chimpanzee adenovirus (ChAdOx1) vector. An analysis of TTS events in the AstraZeneca global safety database, which captures all spontaneously reported AEs from real-world use, reported estimated rates of TTS after the first and second doses

of AZD1222 (Bhuyan 2021). Within 14 days of the first dose, the estimated rate of TTS was 8.1 per million vaccinees, based on approximately 49.23 million first doses administered. Within 14 days of the second dose, the estimated rate of TTS was 2.3 per million vaccinees, based on approximately 5.62 million vaccinees. The very low rate of TTS reported following a second AZD1222 dose was reported to be within preliminary estimates of the background range in an unvaccinated population pre-COVID-19. Given the similarity in the vaccine vectors, the lower rate of TTS following a second dose of AZD1222 compared with the first dose suggests that a similar decrease might be observed after a second dose of Ad26.COV2.S.

6.5. Conclusion

The final analysis of COV3001 demonstrate that the single dose Ad26.COV2.S primary regimen provides substantial protection against severe COVID-19 disease, hospitalization and death and maintains a favorable benefit-risk profile. Durable protection against observed COVID-19 and COVID-19 related hospitalizations was confirmed by large real-world-effectiveness studies in the US and South Africa, including in calender time that the delta variant was highlight prevalent. Therefore, the single dose Ad26.COV2.S regimen continues to be an important tool in the fight against COVID-19.

An Ad26.COV2.S booster dose administered 2 months after the primary Ad26.COV2.S dose substantially increases protection, especially against symptomatic COVID-19, including when caused by SARS-CoV-2 variants of concern.

Studies COV1001 and COV2001 indicate that a larger interval between the primary vaccination with Ad26.COV2.S and a homologous booster dose resulted in a larger increase in humoral immune responses (ELISA titers) versus the 1-dose regimen, for both participants 18-55 years of age and ≥65 years of age, going from a 4-6 fold increase (both age groups) with a 2-month boost to a 12-fold increase with a 6-month boost (younger age group only).

A total of 9,379 participants ≥18 years of age, including 2,383 participants ≥60 years of age, have received 2 doses of Ad26.COV2.S 5×10^{10} vp in clinical studies, with the booster administered after an interval of 2 months to ≥6 months. Overall, Ad26.COV2.S has an acceptable reactogenicity profile after both the first dose and booster, with the reactogenicity post-booster being similar or milder than post-dose 1. No new safety concerns have been identified after an Ad26.COV2.S booster.

In the early stages of a pandemic, a single dose vaccine is an efficient tool to rapidly increase vaccine uptake and reduce the burden on health care systems by preventing severe disease outcomes, especially where supply limitations were present. In the current stage of the pandemic, and given emergence of different variants under certain circumstances, focus may shift to protecting individuals by maximizing and prolonging vaccine-induced protection, not only against severe/critical COVID-19, but also against symptomatic infection, to potentially reduce transmission, and raise immunity to increase the probability of protection against future variants

of concern. This is important in the US, where the low vaccination coverage puts even vaccinated people at risk because of strong circulation of the highly transmissible delta variant.

In conclusion, the goal of the Janssen Ad26.COV2.S vaccine is to provide a vaccine that can be utilized to fight COVID-19 globally. To support this goal, Janssen has randomized, controlled studies demonstrating:

1. The safety and efficacy of a single dose, with strong (75%) and durable protection against severe disease;
2. The safety and efficacy of 2 doses – a booster given 2 months after dose 1 had higher efficacy against symptomatic and severe disease;
3. In COV1001, the safety and immunogenicity of 2 doses (a booster given 6 month after dose 1) had higher humoral immune responses than those observed with the 2-month boost.

The results of these studies support giving a booster at an interval between 2 and >6 months after the first dose depending on several factors including the epidemiologic profile of COVID-19 in a given region, and perhaps most importantly, the benefit/risk assessment for individuals receiving the vaccine. For those at high risk, such as front-line workers and healthcare providers at high risk of exposure, the severely immunocompromised, and those with certain co-morbidities who may have not had a robust immune response to a single dose, our data support a booster administered 2 months after dose 1. The clinical benefit of the booster is clear with higher efficacy against symptomatic and severe disease than that observed with a single dose, providing maximum protection for these high-risk individuals in a short timeframe with no accompanying increase in reactogenicity. For individuals at lower risk of COVID-19 from an occupational and/or health perspective, having a longer interval between doses may provide additional benefit. A booster administered 6 months after dose 1 induced even greater immune responses than those observed with the 2-month boost. A correlate of protection has not been defined; higher responses could lead to even longer lasting protection than that currently observed. Further, no additional safety signals have been observed in study COV3009 to date and this combined with the data from all the Ad26.COV2.S studies support the safety of the regimen. In summary, the benefits of a booster whether given 2 months or ≥6 months post-vaccination are clear. Our data support a schedule that provides the most benefit to individuals based on their risks associated with COVID-19, whether a single dose for efficient pandemic response, a 2-month boost for individuals at high risk of exposure or with specific health risks, or a ≥6-month boost to maximize durable protection. Further, the data to date show no accompanying increase in risk of adverse events.

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8. APPENDICES

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID **Study Status** **Countries**	**Phase** **Study Design** **Study Population** **Primary Objective(s)**	**Total Number of Participants (active /placebo)**	**Study vaccines: Formulation** **(Route of Administration)** **Duration of Treatment**
Ongoing Clinical Studies			
VAC31518COV1001[a] Ongoing Belgium, US	Phase 1/2a First-in-human, randomized, double-blind, placebo-controlled, multicenter Healthy adults aged ≥18 to ≤55 years and ≥65 years[a] To assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM as a single dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions	Planned: 1,045 (860/185)	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on each vaccination day
VAC31518COV1002 Ongoing Japan	Phase 1 Randomized, double-blind, placebo-controlled Healthy adults aged ≥20 to ≤55 years and ≥65 years To assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels, 5×10^{10} vp and 1×10^{11} virus particles (vp), administered IM as 2-dose schedule in healthy adults aged ≥20 to ≤55 years and ≥65 years in good health with or without stable underlying conditions	Planned: 250 (200/50)	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on each vaccination day

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Study ID **Study Status** **Countries**	**Phase** **Study Design** **Study Population** **Primary Objective(s)**	**Total Number of Participants (active /placebo)**	**Study vaccines: Formulation** **(Route of Administration)** **Duration of Treatment**
VAC31518COV2001 Ongoing Adolescent Cohorts: UK and Spain; Adult Cohort (only): Germany, Netherlands, Spain	Phase 2a Randomized, double-blind, placebo-controlled, multicenter Healthy adolescents aged 12 to 17 years, inclusive. Healthy adults aged ≥18 to ≤55 years, and Adults in good or stable health aged ≥65 years To assess the humoral immune response to 3 dose levels (5×10^{10} vp, 2.5×10^{10} vp, 1.25×10^{10} vp) of Ad26.COV2.S, administered as a 2-dose schedule at a 56-day interval, 28 days after Vaccination 2 To assess the humoral immune response to 2 dose levels (1×10^{11} vp and 5×10^{10} vp) of Ad26.COV2.S, administered as a single vaccination, 28 days after Vaccination 1 To assess the humoral immune response to Ad26.COV2.S at the 5×10^{10} vp dose level, administered as a 2-dose schedule at a 28-day and at an 84-day interval, 28 days after Vaccination 2 To assess the safety and reactogenicity of Ad26.COV2.S, administered IM as a 2-dose or a single-dose schedule	<u>Adults:</u> Planned: 550 (475/75) <u>Adolescents:</u> Planned: 33	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on each vaccination day

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Study ID **Study Status** **Countries**	**Phase** **Study Design** **Study Population** **Primary Objective(s)**	**Total Number of Participants (active /placebo)**	**Study vaccines: Formulation** **(Route of Administration)** **Duration of Treatment**
VAC31518COV3001 (ENSEMBLE) Ongoing Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, US	Phase 3 Randomized, double-blind, placebo-controlled, multicenter Stage 1a and 1b: Adults aged ≥18 to <60 years Stage 2a and 2b: Adults aged ≥60 years To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, symptomatic COVID-19 when given as a single-dose vaccination regimen, as compared to placebo, in SARS-CoV-2 seronegative adults	Planned: 40,000 (20,000/ 20,000) Actual: 43,783 (21,895/21,888)	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on each vaccination day
VAC31518COV3009 (ENSEMBLE2)[b] Ongoing Belgium, Brazil, Colombia, France, Germany, Philippines, South Africa, Spain, United Kingdom, US	Phase 3 Randomized, double-blind, placebo-controlled, multicenter Healthy adults aged ≥18 years To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19, as compared to placebo, in SARS-CoV-2 seronegative adults	Planned: 30,000 (15,000/15,000)	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on Day 1 and Day 57 of $5x10^{10}$vp
Recently Initiated Clinical Studies			
VAC31518COV2004 (HORIZON) Ongoing 3 countries	Phase 2 Non-randomized, open-label, multicenter Healthy pregnant (2nd and/or 3rd trimester of pregnancy) participants ≥18 to ≤45 years of age To assess the safety and reactogenicity of a single dose level ($5×10^{10}$ vp) of Ad26.COV2.S, administered IM as a 2-dose schedule, in adult participants	Planned: 400	• Ad26.COV2.S: suspension (IM) Single vaccination on each vaccination day

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID Study Status Countries	Phase Study Design Study Population Primary Objective(s)	Total Number of Participants (active /placebo)	Study vaccines: Formulation (Route of Administration) Duration of Treatment
	during the 2nd and/or 3rd trimester of pregnancy. To assess the humoral immune response in peripheral blood of adult participants to Ad26.COV2.S administered IM as a 1-dose (5×10^{10} vp), or 2-dose (2.5×10^{10} vp) schedule, during the 2nd and/or 3rd trimester of pregnancy, 28 days after the first vaccination and 14 days after the second vaccination.		
VAC31518COV2008 Ongoing US	Phase 2 Randomized, double-blind, parallel, multicenter Adults aged ≥18 years who previously received Ad26.COV2.S primary vaccination in Janssen-sponsored study COV3001 (Cohort 1) or who previously received primary vaccination with the Pfizer BNT162b2 vaccine (Cohort 2). Primary Objective 1: To demonstrate the NI of the neutralizing antibody response to the original strain 14 days after booster vaccination with Ad26.COV2.S at either the $1x10^{10}$ vp, $2.5x10^{10}$ vp or 5×10^{10} vp dose level, administered ≥6 months after single-dose primary vaccination with Ad26.COV2.S (5×10^{10} vp dose level), compared to the neutralizing antibody response to the original strain induced by single-dose primary vaccination with Ad26.COV2.S at the 5×10^{10} vp dose level To demonstrate the NI of the neutralizing antibody response to the leading variant of high consequence or concern* 14 days after booster vaccination with Ad26.COV2.S at the 5×10^{10} vp dose level, administered ≥6 months after single-dose primary vaccination with Ad26.COV2.S (5×10^{10} vp dose level), compared to the neutralizing antibody response to the	Planned:1540 (770 Cohort 1; 770 Cohort 2)	• Ad26.COV2.S: suspension (IM) Single vaccination on each vaccination day

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID Study Status Countries	Phase Study Design Study Population Primary Objective(s)	Total Number of Participants (active /placebo)	Study vaccines: Formulation (Route of Administration) Duration of Treatment
	leading variant of high consequence or concern* induced by single-dose primary vaccination with Ad26.COV2.S at the 5×10^{10} vp dose level, if feasible. Primary Objective 2: To demonstrate the NI of the neutralizing antibody response to the original strain 14 days after booster vaccination with Ad26.COV2.S at either the $1x10^{10}$ vp, $2.5x10^{10}$ vp or 5×10^{10} vp dose level, administered ≥6 months after completing a 2-dose primary vaccination with Pfizer BNT162b2, compared to the neutralizing antibody response to the original strain induced by single-dose primary vaccination with Ad26.COV2.S at the 5×10^{10} vp dose level.		
Planned Clinical Studies			
VAC31518COV3005 Planned 4 countries	Phase 3 Randomized, double-blind, placebo-controlled, parallel, interventional, multicenter Healthy adults aged ≥18 years To demonstrate the NI of the humoral immune response expressed by the GMTs of HI antibody titers against each of the 4 influenza vaccine strains after concomitant administration of the Ad26.COV2.S vaccine and a seasonal quadrivalent high-dose influenza vaccine versus the administration of a seasonal quadrivalent high-dose influenza vaccine administered alone; To demonstrate the NI of the humoral immune response expressed by the GMTs of HI antibody titers against each of the 4 influenza vaccine strains after concomitant administration of the Ad26.COV2.S vaccine and a seasonal quadrivalent standard-dose influenza vaccine versus the administration of a	Planned: 1,680	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on each vaccination day

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID Study Status Countries	Phase Study Design Study Population Primary Objective(s)	Total Number of Participants (active /placebo)	Study vaccines: Formulation (Route of Administration) Duration of Treatment
	seasonal quadrivalent standard-dose influenza vaccine administered alone; To demonstrate the NI of the humoral immune response expressed by the GMCs of ELISA antibody concentration after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent high-dose standard-dose influenza vaccine versus the administration of Ad26.COV2.S vaccine administered alone; To demonstrate the NI of the humoral immune response expressed by the GMCs of ELISA antibody concentration after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent standard-dose influenza vaccine versus the administration of Ad26.COV2.S vaccine administered alone		
VAC31518COV3006 (HORIZON 2) Planned Argentina, Brazil, Columbia, India Mexico, India, South Africa, Thailand and Philippines.	Phase 2/3 Randomized, double-blind, placebo-controlled, pivotal Healthy adolescents aged ≥12 to ≤17 years **Part 1:** To assess the safety, reactogenicity, and humoral immune response of Ad26.COV2.S or placebo administered IM as a 1-dose regimen (at 2.5×10^{10} vp per 0.5 mL, 2.5×10^{10} vp per 0.25 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level) or as a 2-dose (56-day interval) regimen (1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) in adolescents **Part 2:** To assess the safety, reactogenicity, and humoral immune response of Ad26.COV2.S or placebo administered IM as a 1-dose regimen (at 2.5×10^{10} vp per 0.5 mL or 2.5×10^{10} vp per 0.25 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) or as a 2-dose (56-day interval) regimen	Planned: 2,100-4,350	• Ad26.COV2.S: suspension (IM) • Placebo: saline (IM) Single vaccination on each vaccination day

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID **Study Status** **Countries**	**Phase** **Study Design** **Study Population** **Primary Objective(s)**	**Total Number of Participants (active /placebo)**	**Study vaccines: Formulation** **(Route of Administration)** **Duration of Treatment**
	(1.25×10^{10} vp, 0.625×10^{10} vp dose levels and at a lower, to be determined, dose level) in adolescents; To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 2.5×10^{10} vp in adolescents versus 1 dose of Ad26.COV2.S 5×10^{10} vp in young adults from VAC31518COV3001 study (18 to 25 years of age) To demonstrate NI of immune responses induced by 2 doses of Ad26.COV2.S 1.25×10^{10} vp in adolescents versus 1 dose of Ad26.COV2.S 5×10^{10} vp in young adults from VAC31518COV3001 study (If the above is demonstrated, then to demonstrate the following in sequential order).		
Post-authorization Observational Safety Studies			
VAC31518COV4001 Ongoing US	Phase 4 Retrospective observational study Subjects who have at least 1 year of continuous health plan enrollment with medical and prescription drug coverage prior to the reference date and may or may not have had at least 1 dose of Ad26.COV2.S To assess the potential association between the occurrence of predefined AESIs and vaccination with Ad26.COV2.S within disease-specific risk periods in individuals exposed to the vaccine, as compared with unexposed individuals or a control window within the same individual	Not applicable	• Ad26.COV2.S suspension (IM) Single vaccination
VAC31518COV4002 Ongoing US	Phase 4 Longitudinal, observational cohort study	Planned: 100,000	• Ad26.COV2.S suspension (IM) Single vaccination

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID **Study Status** **Countries**	**Phase** **Study Design** **Study Population** **Primary Objective(s)**	**Total Number of Participants (active /placebo)**	**Study vaccines: Formulation** **(Route of Administration)** **Duration of Treatment**
	Adults aged ≥18 years who have at least 12 months of medical history prior to the index date and have at least 1 claim for a health care interaction (medical, pharmacy, and/or laboratory) To estimate the effectiveness of Ad26.COV2.S in preventing any observed COVID-19 (defined as COVID-19 diagnosis and/or positive diagnostic SARS-CoV-2 test) To estimate the effectiveness of Ad26.COV2.S in preventing COVID-19 related hospitalization To estimate the effectiveness of Ad26.COV2.S in preventing all-cause mortality during a COVID-19 related hospitalization		
VAC31518COV4003 Ongoing Europe	Phase 4 Retrospective observational study To assess the potential association between the occurrence of predefined AESIs and vaccination with Ad26.COV2.S within disease-specific risk periods in individuals exposed to the Ad26.COV2.S vaccine compared to COVID-19 vaccine unexposed individuals, or compared to a control window within the same individual	Planned: Not applicable	• Ad26.COV2.S suspension (IM) Single vaccination
VAC31518COV4004 Ongoing Germany, France, Spain, Romania, Poland, Italy, Iceland, Belgium, Finland, UK	Phase 4 Prospective, multicenter, multicountry, hospital-based case-control study Subjects ever eligible for COVID-19 vaccination following the national/regional immunization recommendations prior to hospital	Planned: NA	• Ad26.COV2.S suspension (IM) NA Single vaccination 6 months to 2 years

Appendix 1: Tabular Listing of Planned and Ongoing Clinical Studies with Ad26.COV2.S

Study ID Study Status Countries	Phase Study Design Study Population Primary Objective(s)	Total Number of Participants (active /placebo)	Study vaccines: Formulation (Route of Administration) Duration of Treatment
	admission and are hospitalized and meet the SARI case definition To estimate CVE of COVID-19 Vaccine Janssen against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been vaccinated with a single dose compared with unvaccinated SARI patients		

a. Study sites in Belgium will enroll healthy adults aged ≥18 to ≤55 years and adults aged ≥65 to ≤75 years.
b. The ENSEMBLE 2 study was referred to as the HORIZON study up to IB Edition 2

Note: Ad26.COV2.S was referred to as Ad26COVS1 in IB Edition 1.
Clinical Studies listed above in the Table of Studies as of a cut-of-date of 19 July 2021.
Keys: AESI=adverse event of special interest; BLA= Biologic License Application; CO = cross-over; CoAd = co-administration; COVID-19=Coronavirus disease; CVE= COVID-19 vaccine effectiveness; ELISA= enzyme-linked immunosorbent assay; EUA= Emergency use authorization; GMC= geometric mean concentrations; GMT= geometric mean titers; HCW= healthcare worker; HD = high-dose; HI= hemagglutination inhibition; IB=investigator brochure; IM=intramuscular; n/a=not applicable; NI= non-inferiority; NV=no vaccinations; Q = quadrivalent; SARI= severe acute respiratory infection; SARS-CoV-2= severe acute respiratory syndrome Coronavirus 2; SCRI= self-controlled risk interval; SD = standard-dose; SDL= selected dose level; UK=United Kingdom; US=United States vp= virus particles.

Appendix 2: COVID-19 Severity Case Definitions

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:		**Any 2 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**	• Fever (≥38.0°C or ≥100.4°F) • Heart rate ≥90 beats/minute • Shaking chills or rigors • Sore throat • Cough • Malaise as evidenced by one or more of the following**: o Loss of appetite o Generally unwell o Fatigue o 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.

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) ≤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.

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

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

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.

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.

Appendix 3: Publications Ad26.COV2.S Vaccine Effectiveness – RWE

Study Description	Data Source	Methodology	Results for Ad26.COV2.S	Reference
1. Effectiveness of the single dose Ad26.COV2.S vaccine against severe COVID-19 for Health Care workers in South Africa. The study commenced on 17 February 2021 and completed enrollment on 16 May 2021.	The Sisonke Phase 3B is an open label implementation study sponsored by the South African Medical Research Council. South African health care workers were vaccinated with single-dose Ad26.COV2.S vaccine and followed up during 2 phases of the COVID -19 epidemic; initially during a period dominated by the Beta followed by the Delta variant.	Vaccine effectiveness was analyzed using different approaches including 1) Matched (Retrospective) cohort analysis 2) Test-Negative case control analysis and 3) Adjusted Cohort analysis by calendar time with time-varying vaccination status.	Point estimates for VE derived from three different datasets comprising 245,969 HCWs ranged from 81%-94% to prevent Covid-19 deaths, 71%-85% to prevent severe infections and 67%-84% to prevent hospitalizations. VE remained consistent throughout the Beta and Delta dominant phases of the study.	Bekker 2021 (Manuscript in preparation)
2. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19	Multi-state Mayo Clinic Health System's EHRs; 2/27 to 4/14/2021; Adults aged ≥18 years n = 2,195 (Ad26.COV2.S)	Retrospective analysis of EHRs, 1:10 propensity matching	Vaccine effectiveness of 76.7% (95% CI, 30.3-95.3%) in preventing SARS-CoV-2 infection with onset at least 2 weeks after vaccination.	Corchado-Garcia 2021
3. Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years - COVID-NET, 13 States, February-April 2021	COVID-19-Associated Hospitalization Surveillance Network (COVID-NET); 2/1 to 4/30/2021 Adults aged ≥65 years; n = 7,280 (total for Pfizer-BioNTech, Moderna and Janssen) patients not specified	Poisson regression model	Vaccine effectiveness of 84% (95% CI, 64-93%) in preventing COVID-19 associated hospitalization among adults aged 65-74 years; VE of 85% (95% CI, 72-92%) in preventing COVID-19 associated hospitalization among adults aged ≥75 years.	Moline 2021

Study Description	Data Source	Methodology	Results for Ad26.COV2.S	Reference
4. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings	VISION Network: CDC collaboration with 5 US. health care systems and research centers* Adults aged ≥50 years; n = 1,163 Study Period 01 January 2021 to 22 June 2021.	Test-negative design to estimate vaccine effectiveness	Vaccine effectiveness of Ad26.COV2.S of 68% (95% CI, 50%-79%) against laboratory confirmed SARS-CoV-2 infection leading to hospitalization; vaccine effectiveness of 73% (95% CI, 59%-82%) against infection leading to an emergency department or urgent care clinic visit.	Thompson 2021
5. Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19-Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance - Nine States, June-August 2021	VISION Network 32,867 medical encounters of adults of all ages from June-August 2021	Test-negative design to estimate vaccine effectiveness	Vaccine effectiveness of 60% (95% CI, 31%-77%) against laboratory confirmed SARS-CoV-2 infection leading to hospitalization; vaccine effectiveness of 65% (95% CI, 56%-72%) against infection leading to an emergency department or urgent care clinic visit.	Grannis 2021
6. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, 11 March- 15August 2021	21 hospitals within the Influenza and Other Viruses in the Acutely Ill (IVY) Network, March-August 2021 Adults aged ≥18 years; n = 113	Prospective Case-control analysis	Vaccine effectiveness of 71% (95% CI: 56%-81%) for prevention of COVID-19 hospitalization.	Self 2021

Study Description	Data Source	Methodology	Results for Ad26.COV2.S	Reference
7. Study of COVID-19 Vaccine Breakthrough Infections in Veterans Health Administration	The data source consisted of clinical records of individuals ≥18 vaccinated in the Veterans Health Administration (VHA). AD26.COV2.S vaccine given Jan 1, 2021 through Aug 31, 2021. N=227,570	Retrospective cohort study of vaccine breakthrough infections in fully vaccinated persons in the VHA.	Compared to Ad26.COV2.S, BNT162b2 and mRNA-1273 had lower occurrence of documented SARS-CoV-2 infection (aHR 0.54, 95% confidence interval (CI) 0.51-0.58; aHR 0.36; 95% CI 0.33-0.38; respectively) and COVID-19 hospitalization (aHR 0.56, 95% CI 0.47-0.66; aHR 0.30; 0.25-0.35; respectively).	Sharma 2021
8. Study of COVID-19 vaccine effectiveness against hospitalizations and ICU admissions in the Netherlands, April- August 2021	The data source consisted of all hospitalized persons with a positive SARS-CoV-2 test or CT-confirmed COVID-19 registered in the NICE COVID-19 registry. The study period was 4 April - 29 August 2021.	Incidence rates per 10.000 person-days were calculated. Incidence Rate ratio's (IRR) and 95% CI were estimated with a negative Binomial regression model with log-link function.	Ad26.COV2.S VE of 91% (88%-94%) against hospitalization, n=32.	de Gier 2021

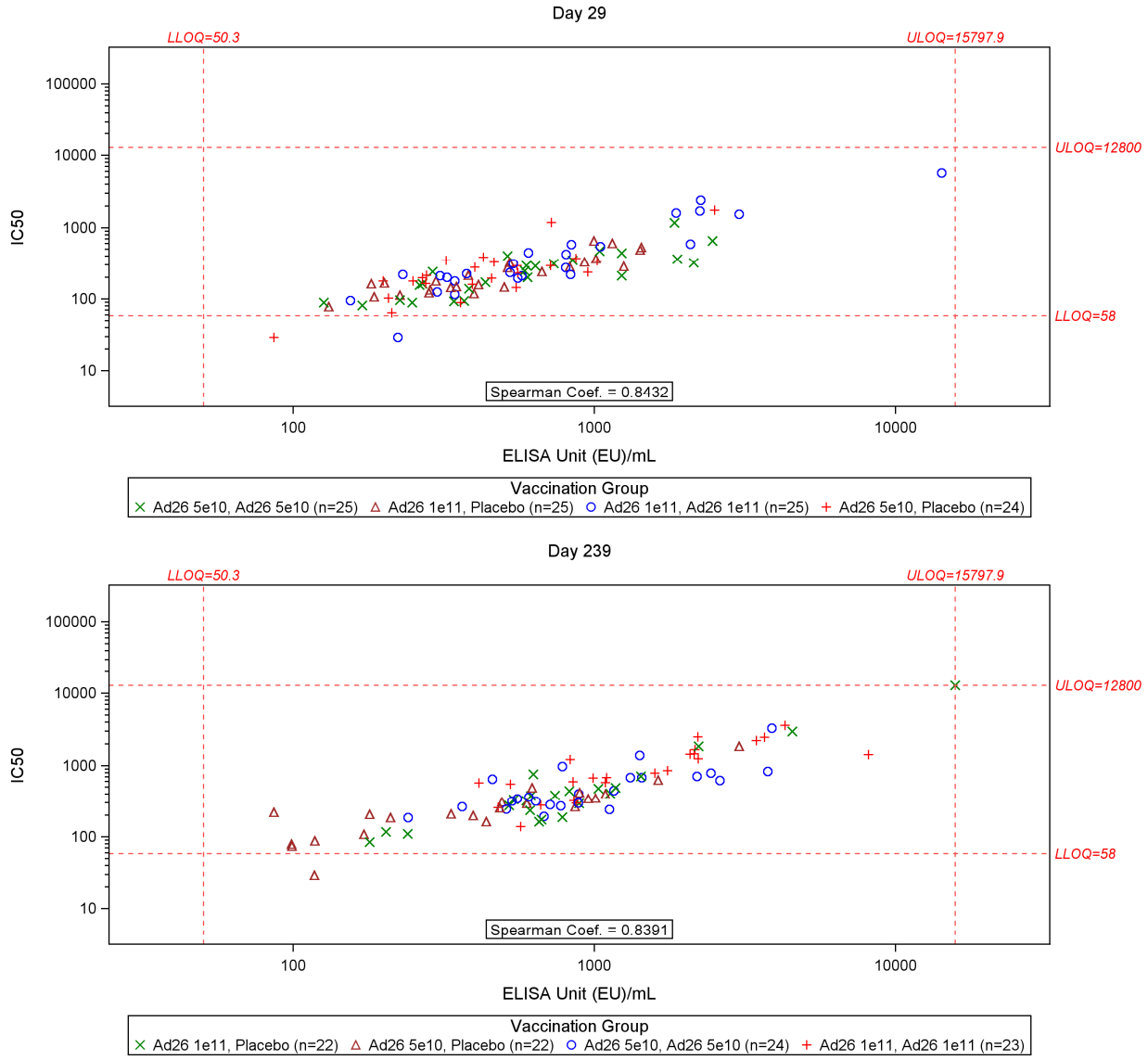
Note: For comparative effectiveness studies, only Ad26.COV2.S COVID-19 Vaccine data are described

*Estimates of the effectiveness of Ad26.COV2.S were limited to 5 network partners with Ad26.COV2.S vaccine recipients (CUIMC, Intermountain Healthcare, KPNC, KPNW and Regenstrief Institute).

ABBREVIATIONS: aHR= adjusted hazard ratio; CDC= Centers for Disease Control & Prevention; CI= confidence interval; ECA= external control arm; EHR= electronic health record; ECMO= extracorporeal membrane oxygenation; IMV= invasive mechanical ventilation; HCW= health care worker; HIPAA= Health Insurance Portability and Accountability Act; HR= hazard ratio; ICU= intensive care unit; IRR= incidence rate ratio; NAAT= nucleic acid amplification test; PCR= Polymerase chain reaction; RCT= randomized controlled trial; RWD= real-world data; VE= vaccine effectiveness; VHA= Veterans Health Administration

Appendix 4: Supportive Data for Study VAC31518COV1001

Figure 25: SARS-CoV-2 Binding Antibodies S ELISA (ELISA Unit (EU)/mL) vs SARS-CoV-2 Neutralization Wild Type VNA - VICTORIA/1//2020 (IC50): Correlation Plots; Cohort 1a; Per Protocol Immunogenicity Set (Study VAC31518COV1001)



The status of the S ELISA assay is: qualified. The assay range may change as the assay becomes validated., The status of the wt VNA Victoria assay is: qualified. The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp.

Adapted from [girhum77-c1a.rtf] [Findings/is/pgm/is25.sas] 27AUG2021, 8:31:20AM SAS 9.4

Figure 26: SARS-CoV-2 Binding Antibodies S ELISA (EU//mL) vs SARS-CoV-2 Neutralization wtVNA - VICTORIA/1/2020 (IC50): Correlation Plots; Cohort 3; Full Analysis PPI Set (Study VAC31518COV1001)

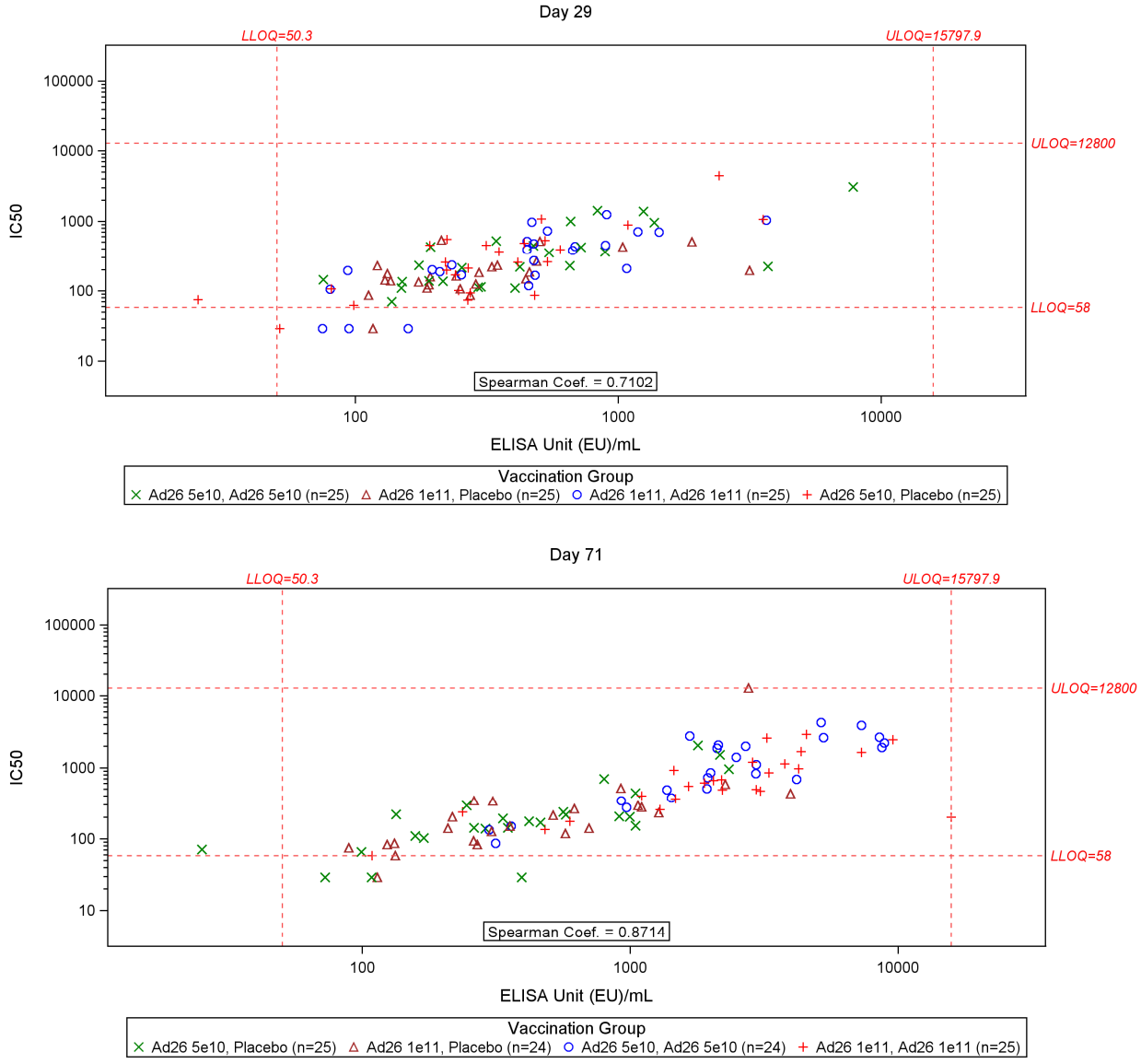
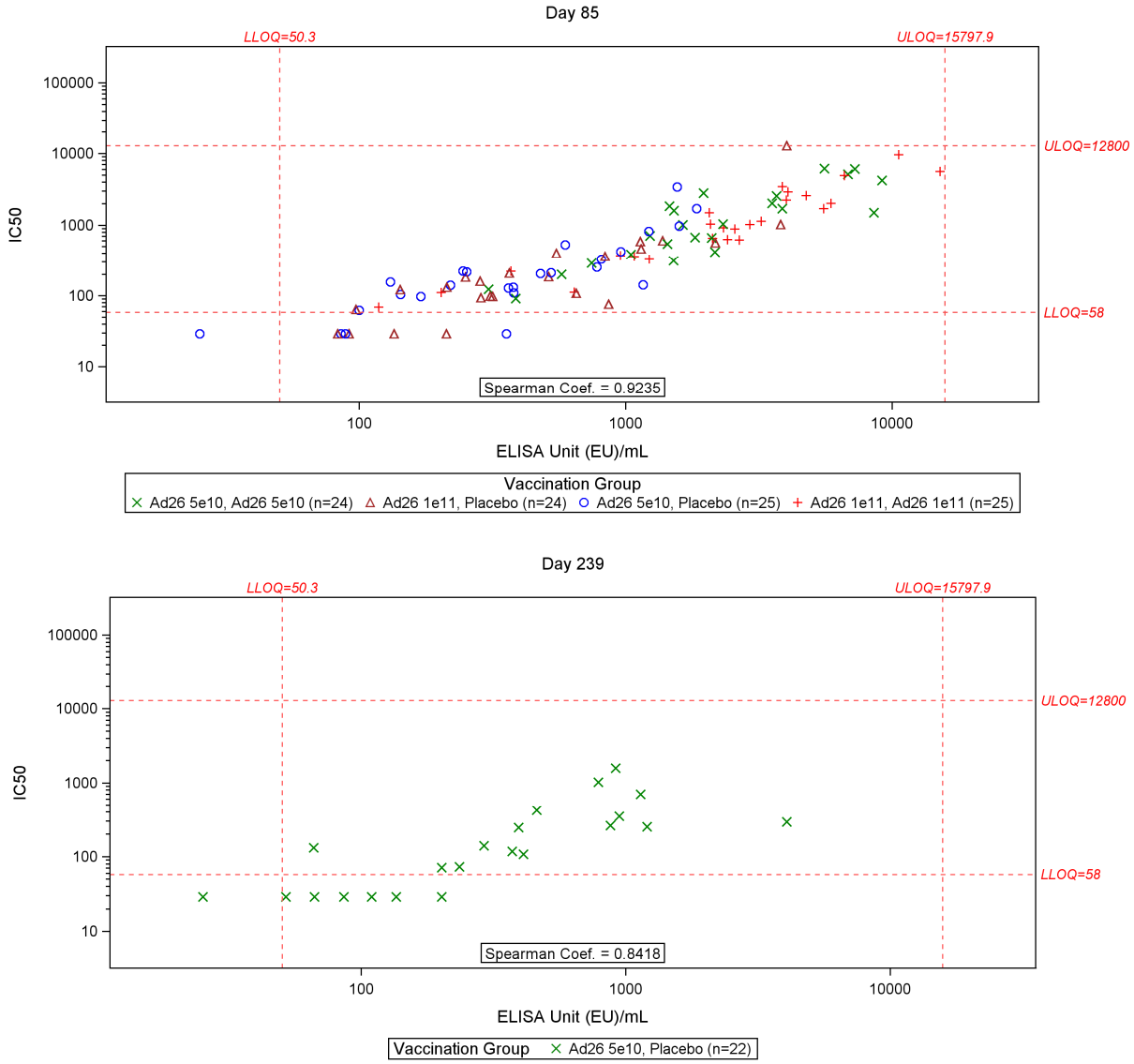


Figure 26: SARS-CoV-2 Binding Antibodies S ELISA (EU//mL) vs SARS-CoV-2 Neutralization wtVNA - VICTORIA/1/2020 (IC50): Correlation Plots; Cohort 3; Full Analysis PPI Set (Study VAC31518COV1001)



The status of the S ELISA assay is: qualified. The assay range may change as the assay becomes validated., The status of the wt VNA Victoria assay is: qualified. The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp.

[girhum77-c3.rtf] [Findings/is/pgm/is25.sas] 27AUG2021, 8:32:57AM SAS 9.4

Figure 27: SARS-CoV-2 neutralization wild type VNA - VICTORIA/1/2020 (IC50) vs SARS-CoV-2 ADCP (Phagocytic Score): Correlation Plots; Cohort 1a; Per Protocol Immunogenicity Set (Study VAC31518COV1001)

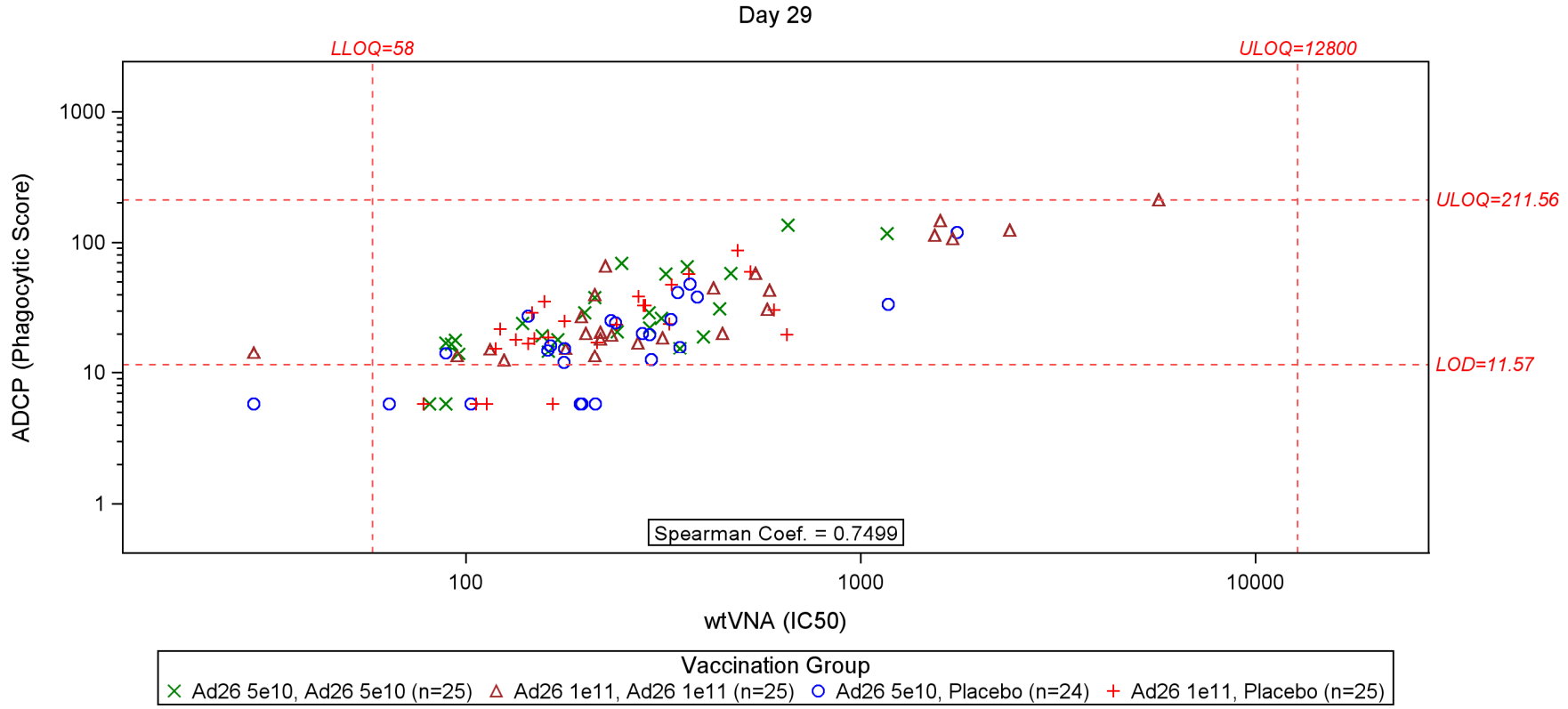
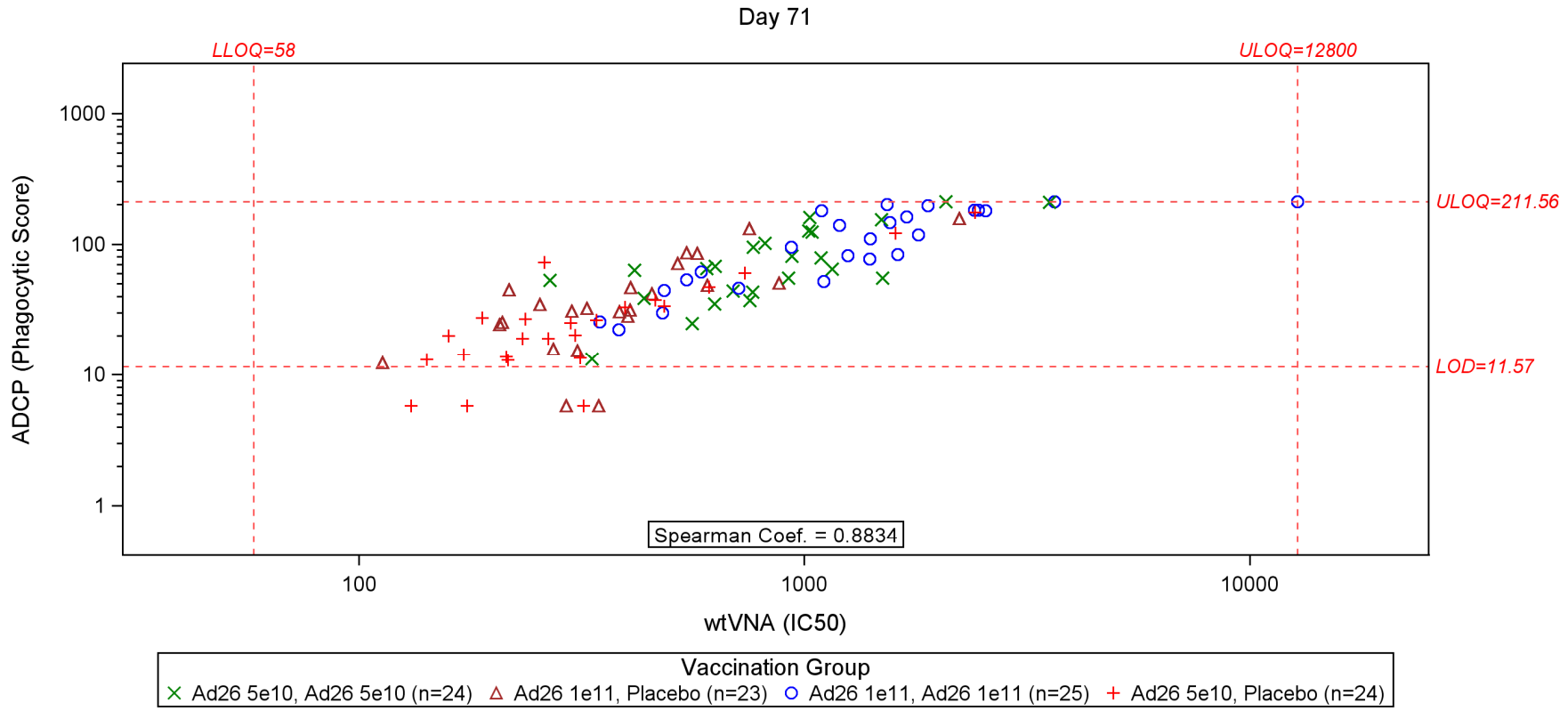


Figure 27: SARS-CoV-2 neutralization wild type VNA - VICTORIA/1/2020 (IC50) vs SARS-CoV-2 ADCP (Phagocytic Score): Correlation Plots; Cohort 1a; Per Protocol Immunogenicity Set (Study VAC31518COV1001)



The status of the wt VNA Victoria assay is: qualified. The assay range may change as the assay becomes validated., The status of the ADCP assay is: qualified. The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp.

[girhum97-c1a.rtf] [Findings/is/pgm/is25.sas] 25AUG2021, 4:48:17PM SAS 9.4

Figure 28: SARS-CoV-2 binding antibodies S ELISA (ELISA Unit (EU)/mL) vs SARS-CoV-2 ADCP (Phagocytic Score): Correlation Plots; Cohort 1a; Per Protocol Immunogenicity Set (Study VAC31518COV1001)

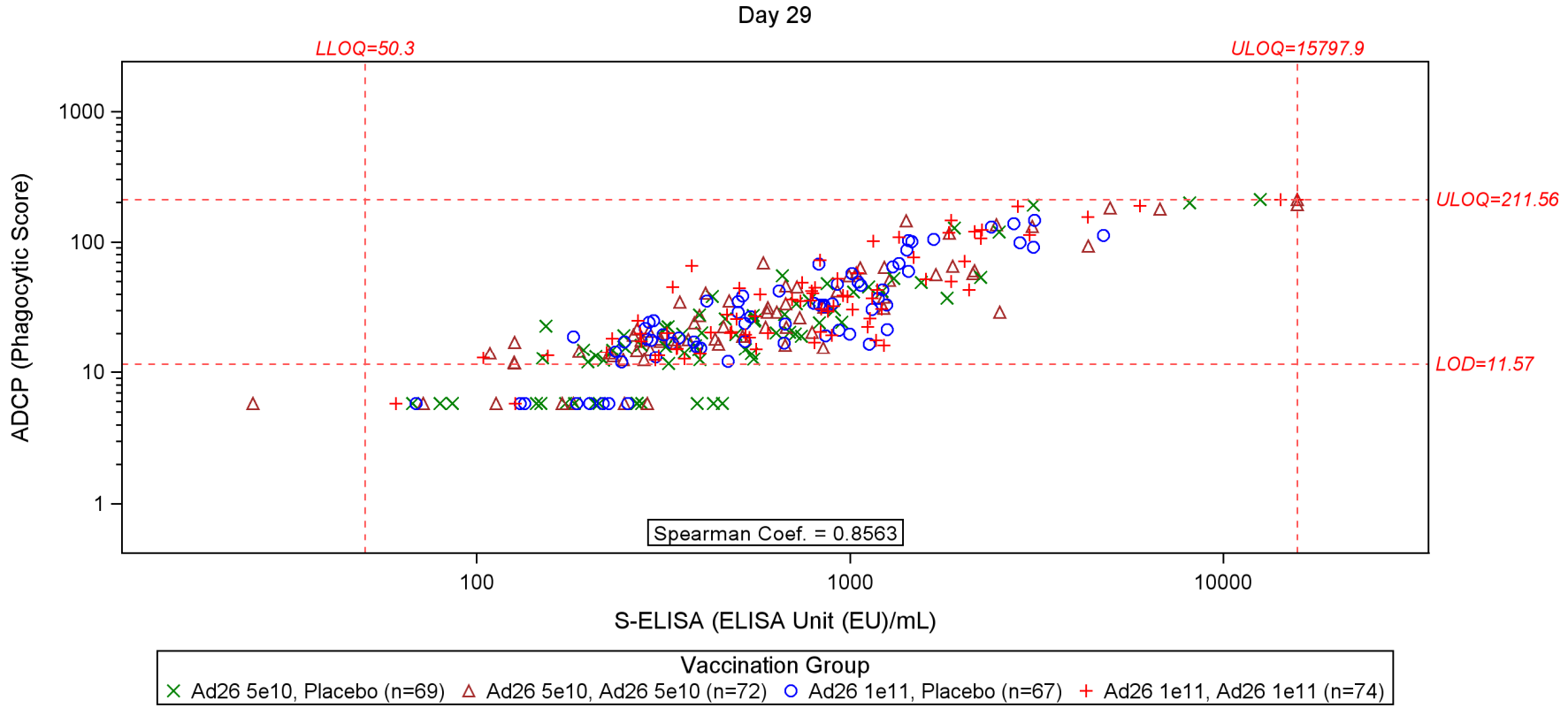
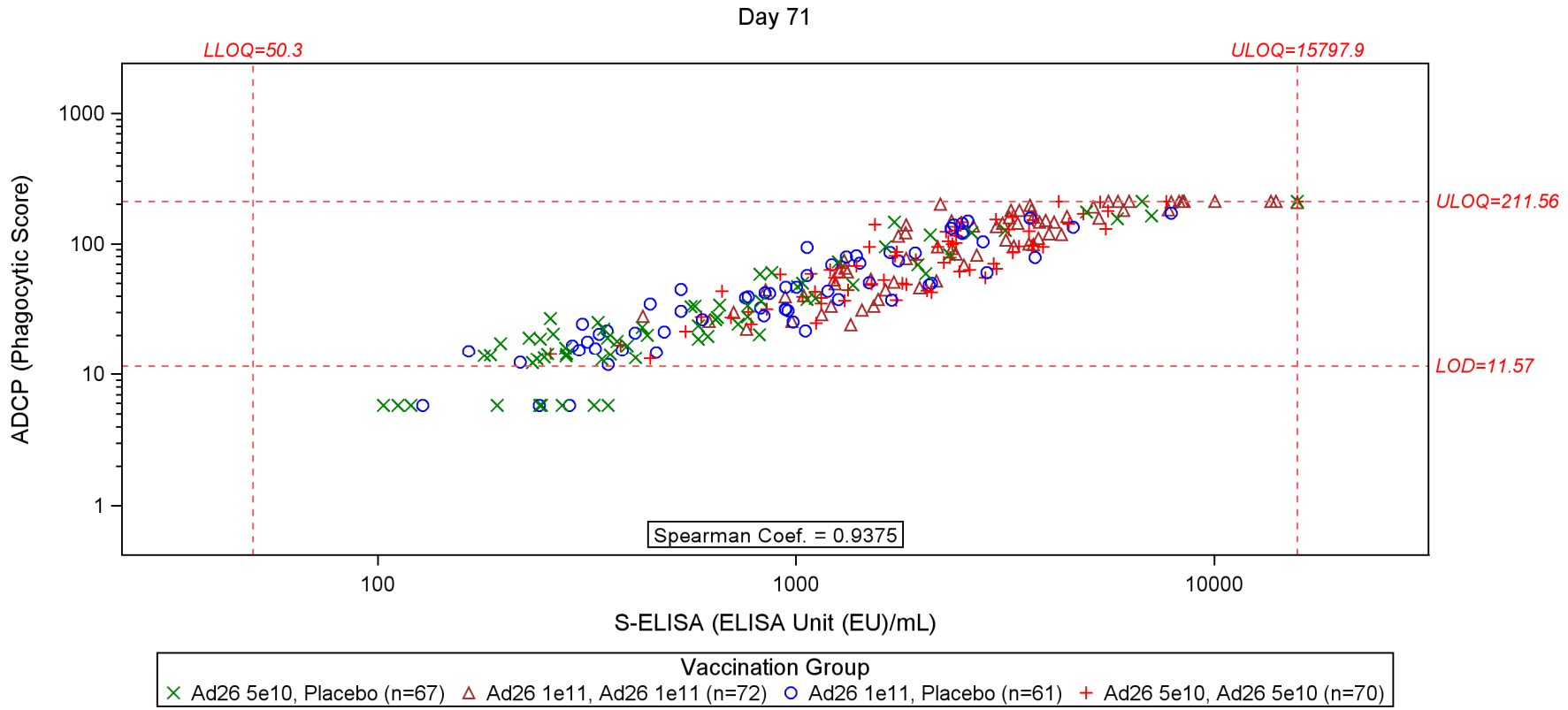


Figure 28: SARS-CoV-2 binding antibodies S ELISA (ELISA Unit (EU)/mL) vs SARS-CoV-2 ADCP (Phagocytic Score): Correlation Plots; Cohort 1a; Per Protocol Immunogenicity Set (Study VAC31518COV1001)



The status of the S ELISA assay is: qualified. The assay range may change as the assay becomes validated., The status of the ADCP assay is: qualified. The assay range may change as the assay becomes validated.
Note: Ad26 5e10: Ad26.COV2.S 5×10^{10} vp; Ad26 1e11: Ad26.COV2.S 1×10^{11} vp.

[girhum98-c1a.rtf] [Findings/is/pgm/is25.sas] 25AUG2021, 4:48:30PM SAS 9.4

Appendix 5: Incidence and Vaccine Effectiveness for COVID-19 and COVID-19-related Hospitalizations, Nationally and by Subgroup

	Vaccinated group			Unvaccinated group			Observed (uncorrected for vaccine under-recording)		Corrected for vaccine under-recording	
	N events	Person-years	Incidence rate	N events	Person-years	Incidence rate	HR (95% CI)	VE (95% CI)	HR (95% CI)	VE (95% CI)
National cohort										
Any observed COVID-19	2,632	141,717	18.57	25,749	481,083	53.52	0.34 (0.33, 0.36)	66% (64%, 67%)	0.24 (0.23, 0.25)	76% (75%, 77%)
COVID-19-related hospitalization	440	142,047	3.10	5,245	484,198	10.83	0.28 (0.26, 0.31)	72% (69%, 74%)	0.19 (0.18, 0.22)	81% (78%, 82%)
Subgroups within National Cohort										
Age < 50										
Any observed COVID-19	912	46,720	19.52	10,322	156,973	65.76	0.29 (0.27, 0.31)	71% (69%, 73%)	0.20 (0.18, 0.21)	80% (79%, 82%)
COVID-19-related hospitalization	62	46,842	1.32	1,033	158,331	6.52	0.20 (0.16, 0.26)	80% (74%, 84%)	0.13 (0.11, 0.17)	87% (83%, 89%)
Age >= 50										
Any observed COVID-19	1,720	94,997	18.11	15,409	323,952	47.57	0.38 (0.36, 0.40)	62% (60%, 64%)	0.27 (0.25, 0.28)	73% (72%, 75%)
COVID-19-related hospitalization	378	95,205	3.97	4,112	325,707	12.62	0.31 (0.28, 0.35)	69% (65%, 72%)	0.21 (0.19, 0.24)	79% (76%, 81%)
Age < 60										
Any observed COVID-19	1,563	77,955	20.05	15,847	260,100	60.93	0.33 (0.31, 0.34)	67% (66%, 69%)	0.23 (0.21, 0.23)	77% (77%, 79%)
COVID-19-related hospitalization	132	78,167	1.69	2,086	262,163	7.96	0.21 (0.18, 0.25)	79% (75%, 82%)	0.14 (0.12, 0.17)	86% (83%, 88%)
Age >= 60										
Any observed COVID-19	1,069	63,762	16.77	9,900	220,795	44.84	0.37 (0.35, 0.39)	63% (61%, 65%)	0.26 (0.25, 0.27)	74% (73%, 75%)

	Vaccinated group			Unvaccinated group			Observed (uncorrected for vaccine under-recording)		Corrected for vaccine under-recording	
	N events	Person-years	Incidence rate	N events	Person-years	Incidence rate	HR (95% CI)	VE (95% CI)	HR (95% CI)	VE (95% CI)
COVID-19-related hospitalization	308	63,880	4.82	3,081	221,851	13.89	0.35 (0.31, 0.39)	65% (61%, 69%)	0.24 (0.22, 0.27)	76% (73%, 78%)
Age < 65										
Any observed COVID-19	1,880	97,790	19.22	19,155	325,147	58.91	0.32 (0.31, 0.34)	68% (66%, 69%)	0.22 (0.21, 0.23)	78% (77%, 79%)
COVID-19-related hospitalization	188	98,044	1.92	2,862	327,629	8.74	0.22 (0.19, 0.25)	78% (75%, 81%)	0.15 (0.13, 0.17)	85% (83%, 87%)
Age >= 65										
Any observed COVID-19	752	43,927	17.12	6,722	155,775	43.15	0.39 (0.37, 0.42)	61% (58%, 63%)	0.28 (0.26, 0.30)	72% (70%, 74%)
COVID-19-related hospitalization	252	44,004	5.73	2,350	156,437	15.02	0.38 (0.33, 0.43)	62% (57%, 67%)	0.26 (0.23, 0.30)	74% (70%, 77%)
Immunocompromised										
Any observed COVID-19	246	9,915	24.81	1,753	34,969	50.13	0.49 (0.43, 0.56)	51% (44%, 57%)	0.36 (0.32, 0.41)	64% (59%, 68%)
COVID-19-related hospitalization	68	9,946	6.84	519	35,183	14.75	0.46 (0.36, 0.60)	54% (40%, 64%)	0.33 (0.26, 0.43)	67% (57%, 74%)
Not immunocompromised										
Any observed COVID-19	2,386	131,802	18.10	23,971	446,039	53.74	0.33 (0.32, 0.35)	67% (65%, 68%)	0.23 (0.22, 0.24)	77% (76%, 78%)
COVID-19-related hospitalization	372	132,101	2.82	4,603	448,944	10.25	0.27 (0.25, 0.30)	73% (70%, 75%)	0.18 (0.17, 0.20)	82% (80%, 83%)
HIV Positive										
Any observed COVID-19	14	576	24.33	68	2,072	32.82	0.74 (0.42, 1.32)	26% (-32%, 58%)	1.11 (0.63, 1.98)	-11% (-98%, 37%)

	Vaccinated group			Unvaccinated group			Observed (uncorrected for vaccine under-recording)		Corrected for vaccine under-recording	
	N events	Person-years	Incidence rate	N events	Person-years	Incidence rate	HR (95% CI)	VE (95% CI)	HR (95% CI)	VE (95% CI)
COVID-19-related hospitalization	4	578	6.92	26	2,079	12.51	0.56 (0.20, 1.61)	44% (-61%, 80%)	0.56 (0.20, 1.61)	44% (-61%, 80%)
Not HIV Positive										
Any observed COVID-19	2,618	141,142	18.55	25,808	479,065	53.87	0.34 (0.33, 0.36)	66% (64%, 67%)	0.24 (0.23, 0.25)	76% (75%, 77%)
COVID-19-related hospitalization	436	141,470	3.08	5,206	482,186	10.80	0.28 (0.26, 0.31)	72% (69%, 74%)	0.19 (0.18, 0.21)	81% (79%, 82%)
Type 2 Diabetes										
Any observed COVID-19	592	22,417	26.41	4,524	76,702	58.98	0.45 (0.41, 0.49)	55% (51%, 59%)	0.33 (0.30, 0.36)	67% (64%, 70%)
COVID-19-related hospitalization	159	22,483	7.07	1,524	77,182	19.75	0.36 (0.30, 0.42)	64% (58%, 70%)	0.26 (0.21, 0.30)	74% (70%, 79%)
No Type 2 Diabetes										
Any observed COVID-19	2,040	119,300	17.10	21,234	404,307	52.52	0.32 (0.31, 0.34)	68% (66%, 69%)	0.22 (0.21, 0.23)	78% (77%, 79%)
COVID-19-related hospitalization	281	119,564	2.35	3,643	406,970	8.95	0.26 (0.23, 0.30)	74% (70%, 77%)	0.18 (0.15, 0.20)	82% (80%, 85%)
High-Delta-incidence States*										
Any observed COVID-19	372	10,691	34.80	3,466	36,564	94.79	0.36 (0.32, 0.40)	64% (60%, 68%)	0.25 (0.22, 0.28)	75% (72%, 78%)
June - Aug 2021 Only**	327	7,399	44.2	2,948	24,814	118.8	0.37 (0.33, 0.41)	63% (59%, 67%)	0.26 (0.23, 0.29)	74% (71%, 77%)
COVID-19-related hospitalization	61	10,726	5.69	718	36,910	19.45	0.29 (0.22, 0.37)	71% (63%, 78%)	0.20 (0.15, 0.25)	80% (75%, 85%)
June - Aug 2021 Only**	49	7,431	6.59	592	25,127	23.56	0.28 (0.21, 0.37)	72% (63%, 79%)	0.19 (0.14, 0.25)	81% (75%, 86%)

	Vaccinated group			Unvaccinated group			Observed (uncorrected for vaccine under-recording)		Corrected for vaccine under-recording	
	N events	Person-years	Incidence rate	N events	Person-years	Incidence rate	**HR (95% CI)**	**VE (95% CI)**	**HR (95% CI)**	**VE (95% CI)**
Sensitivity Analyses										
SA1: Lab-only outcomes among National Cohort										
Any observed COVID-19 (lab only)	383	142,064	2.70	3,630	484,495	7.49	0.36 (0.32, 0.40)	64% (60%, 68%)	0.25 (0.22, 0.28)	75% (72%, 78%)
COVID-19-related hospitalization (lab only)	6	142,124	0.04	127	485,055	0.26	0.16 (0.07, 0.37)	84% (63%, 93%)	0.10 (0.04, 0.24)	90% (76%, 96%)
SA2: Individuals from National cohort meeting data extraction criteria prior to cohort entry* **										
Any observed COVID-19	1,585	63,258	25.06	9,635	225,770	42.68	0.59 (0.56, 0.62)	41% (38%, 44%)	0.46 (0.44, 0.48)	54% (52%, 56%)
COVID-19-related hospitalization	242	63,469	3.81	1,808	226,988	7.97	0.48 (0.42, 0.55)	52% (45%, 58%)	0.37 (0.32, 0.42)	63% (58%, 68%)

Unless otherwise noted, incident rates are reported per 1,000 person-years and vaccine effectiveness (VE) estimates (observed and corrected) are calculated using hazard ratios with reported 95% confidence interval limits. Corrected VE estimates are adjusted for under-recording of vaccinations in claims data assuming sensitivity of vaccine capture in claims data as 60% (40% under-recording).
* High-Delta-incidence States (early Delta states) include Arkansas, Florida, Louisiana, and Missouri.
** For June-Aug 2021 results within four states (Arkansas, Florida, Louisiana, and Missouri) with high prevalence of the Delta variant of concern, incident rate ratios (IRR) after PS matching are reported instead of hazard ratios and VE is estimated using (1-IRR)x100 for patients contributing follow-up time from June 1, 2021 through Aug 31, 2021.
***Footnote summarizing data pull criteria: Patients were eligible for inclusion in the dataset if they met any of the following criteria between 12/1/2019 through most recent data collection. For eligible patients, all records were included from 12/1/2018 forward: 1. ICD-10 codes for the following diagnoses found in the medical claims or chargemaster data: Influenza-like illness, Upper respiratory, Influenza, Pneumonia, COVID-19, Cough, Shortness of Breath, Fever, ARDS, Diarrhea, Fatigue, Sputum/Hemoptysis, Hypoxia 2. The following procedures codes found in the medical claims or chargemaster data: COVID-19 NAAT lab order, COVID-19 Antibody lab order, Bevacizumab, Tocilizumab, Interferon beta-1a, Eculizumab, Siltuximab 3. The following treatments found in the pharmacy claims or chargemaster data: Oseltamivir, Chloroquine, Hydroxychloroquine, lopinavir/ritonavir, Tocilizumab, Sarilumab, Baricitinib, baloxavir marboxil, emtricitabine/tenofovir disoproxil fumarate, darunavir and cobicistat, interferon beta-1a, Fingolimod, Eculizumab, Aliskiren, Anakinra, angiotensin II, Emapalumab-lzsg, lucinactant (surfaxin), Ruxolitinib, Siltuximab, Caplacizumab, Dupilumab 4. COVID-19 antibody or NAAT lab tests 5. COVID-19 vaccinated in medical/pharmacy data between 12/1/2020 through most recent data collection Note patients with confirmed COVID-19 (COVID-specific diagnosis code or positive NAAT result) before cohort entry were excluded from sensitivity cohorts.