From: Arnold Monto [asmonto@umich.edu]
Sent: 3/12/2021 2:56:34 PM
To: Gruber, Marion [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=019cd2669c7048f7a116d72b7682de44-gruber]
CC: Atreya, Prabhakara [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f96e446284da421a91a4479bb6e553c1-AtreyaP]; Hayes, Kathleen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fb93ef79b3474f7099917a7d1ed56be9-Kathleen.Ha]
Subject: [EXTERNAL] Fwd: J&J Ad26 vaccine efficacy; Al Kapikian's 1975 coronavirus review and baseball comments
Attachments: J&J-02.26.21-Ad26FDA brfng doc.pdf; Kapikian Dev Biol Stand 1975.pdf; 01 Track 1.wma

Dr Davidson found my home phone number and called I had not responded to his emails I said I would forward this to you I explained how things work to him and even tried to explain the numbers issue that concerned him to no avail. This gets me off the hook, and I told him you would not be able to respond. Turns out he knew Al Kapikian at NIH and the rotavirus vaccine stories, which explain the attachments

Regards

Arnold

---------- Forwarded message ---------
From: **Bruce Davidson** <(b) (6)>
Date: Wed, Mar 10, 2021 at 7:50 PM
Subject: J&J Ad26 vaccine efficacy; Al Kapikian's 1975 coronavirus review and baseball comments
To: <asmonto@umich.edu>

Thanks for speaking with me, Dr Monto. If FDA provides the data, I hope you'll forward it. I've tried FDA, 4 different people, at least 7 emails and 4 or 5 phone calls--no answer. None from CDC either.

To be most helpful, additional data should describe, for the 28-day outcome, for the per-protocol patient set (not the safety set, not the enrolled ITT set) both the 18 cases among 1624 vaccinees and 26 cases among 1604 placebo recipients by these descriptors:

	Ad26 cases n=18	Ad26 non-cases n=1610	Placebo cases n=26	Placebo non-cases n=1578
US-resident American Indians				
US-resident Alaska Natives				
Non-US resident American Indians				
Non-US resident Alaska Natives				
Totals	18	1610	26	1578

--

If you look at Table 12 page 28 in the FDA briefing document I've attached for your convenience, you'll see that with 1/3 fewer patients in the "Multiple (mixed) Race" group, the efficacy was just fine, with 95% confidence

limits nowhere near zero, let alone into negative numbers, and without a significant p-value for being different from efficacy in the rest of study subjects.

I've also attached Al Kapikian's coronavirus review (he devised the nomenclature for classifying rhinoviruses, he told me) and his great phone call to the baseball radio station about not allowing blocking home plate. That rule was passed shortly after he died.

Sincerely,

Bruce

--
Bruce L Davidson MD MPH

Email (b) (6)
Tel

--
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Vaccines and Related Biological Products Advisory Committee Meeting
February 26, 2021

FDA Briefing Document

Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19

Sponsor:
Janssen Biotech, Inc.

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Glossary

Ad26	adenovirus type 26
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	chemistry, manufacturing and control
CT	computed tomography
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
LMP	last menstrual period
MAAE	medically attended adverse event
MERS-CoV	Middle Eastern respiratory syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical Resource Utilization
PT	preferred term
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standard MedDRA query
SAP	statistical analysis plan
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
vp	viral particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On February 4, 2021, Janssen Biotech, Inc. (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational vaccine intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine, known as Ad26.COV2.S, is a replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein. The proposed use under an EUA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is a single intramuscular injection at the dose level of 5×10^{10} viral particles (vp).

In support of their EUA request, Janssen has submitted safety and efficacy data from an ongoing multi-national Phase 3 randomized, double-blind and placebo-controlled trial of a single dose ($5x10^{10}$ vp) of Ad26.COV2.S in approximately 40,000 participants. The EUA request followed a successful protocol-specified primary analysis that evaluated co-primary efficacy endpoints of molecularly confirmed, moderate to severe/critical COVID-19 with onset at least 14 and 28 days, respectively, after vaccination in participants without evidence of SARS-CoV-2 infection prior to vaccination. The co-primary efficacy analysis (data cutoff of January 22, 2021) included 39,321 randomized (1:1) participants with a median follow-up time of 2 months post-vaccination. These participants were included in the per-protocol efficacy analysis population.

Vaccine efficacy (VE) against central laboratory-confirmed moderate to severe/critical COVID-19 across all geographic areas in which the trial was conducted was 66.9% (95% CI 59.0, 73.4) when considering cases occurring at least 14 days after the single-dose vaccination and 66.1% (55.0, 74.8) when considering cases occurring at least 28 days after vaccination. For the vaccine and placebo groups, respectively, there were 116 and 348 COVID-19 cases that occurred at least 14 days after vaccination, and 66 and 193 cases that occurred at least 28 days after vaccination. Analyses of secondary endpoints demonstrated vaccine efficacy against central laboratory confirmed and blind-adjudicated severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination of 76.7% (54.6, 89.1) and 85.4% (54.2, 96.9), respectively. VE estimates for prevention of moderate to severe/critical COVID-19 and for prevention of severe/critical COVID-19 including positive PCR results still awaiting confirmation by the central laboratory were similar (but with narrower confidence intervals) to the VE estimates that included only centrally-confirmed cases. In a post hoc analysis of all COVID-19 related hospitalizations starting 14 days after vaccination, including non-centrally confirmed cases, there were 2 cases in the vaccine group (with no cases after 28 days) compared with 29 cases in the placebo group (with 16 cases after 28 days). As of February 5, 2021, there were 7 COVID-19 related deaths in the study in the placebo group and no COVID-19 related deaths in the vaccine group.

In general, VE among the subgroups (age, comorbidity, race, ethnicity) appears to be similar to the VE in the overall study population. A lower VE estimate was observed for the subgroup of participants 60 years of age and older with comorbidities compared with the overall population, but with an observed trend of increasing VE with narrower confidence intervals as numbers of cases included in the analysis increased (i.e., counting cases from 14 days rather than 28 days and including cases not yet centrally confirmed). There were no COVID-19-related deaths and no COVID-19 cases requiring medical intervention occurring 28 days or more post-vaccination among participants age 60 years or older with medical comorbidities in the vaccine group. The VE results for some other subgroups with small numbers of participants (≥75 years of age, certain racial subgroups) have limited interpretability. Data were insufficient to assess VE in participants with evidence of prior SARS-CoV-2 infection.

There was country-to-country variation in VE estimates for the prevention of moderate to severe/critical COVID-19 and severe/critical COVID-19, but the confidence intervals were overlapping. Predominant strains among those sequenced were Wuhan-H1 variant D614G in the U.S. (96.4% of sequenced cases), 20H/501Y.V2 variant (B.1.351) in South Africa (94.5% of sequenced cases), and variant of the P.2 lineage in Brazil (69.4% of sequenced cases, with the remaining 30.6% Wuhan-H1 variant D614G). There were no cases identified as B.1.1.7 or P1 lineages as of February 12, 2021.

Safety analysis through the January 22, 2021 data cutoff included 43,783 randomized (1:1) participants ≥18 years of age with 2-month median follow-up. The analysis supported a favorable safety profile with no specific safety concerns identified that would preclude issuance of an EUA.

A subset of participants (N=6,736) was followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. The most common solicited adverse reactions associated with Ad26.COV2.S were injection site pain (48.6%), headache (38.9%), fatigue (38.2%), and myalgia (33.2%); these were predominately mild and moderate, with 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, reported as grade 3. Reports of solicited reactions were less common among participants ≥60 years of age. Reactogenicity to Ad26.COV2.S in adults ≥18 years of age was demonstrated to be transient, and most solicited adverse events (AEs) generally resolved in 1 to 2 days post-vaccination. There were no meaningful imbalances between vaccine and placebo recipients in unsolicited adverse events reported during the 28 days following vaccination.

Among all adverse events collected through the January 22, 2021 data cutoff, a numerical imbalance was seen in non-serious urticaria events reported in the vaccine group (n=5) compared to placebo group (n=1) within 7 days following vaccination which is possibly related to the vaccine. Numerical imbalances were observed between vaccine and placebo recipients for thromboembolic events (15 versus 10) and tinnitus (6 versus 0). Data at this time are insufficient to determine a causal relationship between these events and the vaccine. There were no other notable patterns or numerical imbalances in the available data as of the cutoff date between treatment groups for specific categories of adverse events that would suggest a causal relationship to Ad26.COV2.S.

Non-fatal serious adverse events, excluding those attributed to COVID-19, were infrequent and balanced between study groups with respect to rates and types of events (0.4% in both groups). One serious event of a hypersensitivity reaction, not classified as anaphylaxis, beginning two days following vaccination was likely related to receipt of the vaccine.

There was more frequent, generally mild to moderate reactogenicity in participants 18 to 59 years of age compared to older participants. There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Occurrence of solicited, unsolicited, and serious adverse events in these subgroups was generally consistent with the overall study population.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations whether, based on the totality of scientific evidence available, the benefits of the Ad26.COV2.S vaccine outweigh its risks for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of February 17, 2021, has caused more than 110 million cases of COVID-19 and claimed the lives of more than 2.4 million people worldwide. In the United States, more than 27 million cases and 486,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. FDA issued emergency use authorizations for two mRNA vaccines, developed by Pfizer and Moderna, respectively, in December 2020. Other COVID-19 vaccines currently in development are based on various platforms and include mRNA, DNA, viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 EUA Request for the Janssen Ad26.COV2.S Vaccine

Janssen Biotech, Inc. is developing a replication-incompetent adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein, to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. The Ad26.COV2.S vaccine is administered as a single intramuscular injection of $5x10^{10}$ vp. The vaccine is supplied as a multidose vial (5 doses) containing a refrigerated suspension with a shelf life of 3 months when stored at 2° to 8° C. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial of the single-dose Ad26.COV2.S in approximately 40,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. The primary analysis of 39,321 participants using a data cutoff date of January 22, 2021 demonstrated vaccine efficacy (VE) of 66.9% (adjusted 95% CI 59.0%, 73.4%) for the prevention of moderate to severe/critical COVID-19 occurring at least 14 days vaccination, and

66.1% (adjusted 95% CI 55.0%, 74.8%) for the prevention of cases occurring at least 28 days after vaccination. Safety data from a January 22, 2021 data cutoff with a median of 58 days follow-up after vaccination were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On February 4, 2021, Janssen Biotech, Inc. submitted an EUA request to FDA, based on the primary analyses described above, for Ad26.COV2.S for active immunization for the prevention of COVID-19 in adults 18 years of age and older.

2.3 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4 Available Vaccines and Therapies for COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and

older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under EUA, but not FDA approved, for treatment of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older, administered as 2 doses 3 weeks apart. On December 18, 2020, FDA issued an EUA for the Moderna COVID-19 vaccine for use in individuals 18 years of age and older, administered as 2 doses 4 weeks apart. These COVID-19 vaccines are considered unapproved products, and current supplies are insufficient to vaccinate all persons in the U.S. for whom use of the vaccines are authorized. Thus, there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

2.5 Applicable Guidance for Industry

An EUA for a COVID-19 vaccine allows for the rapid and widespread deployment for administration to millions of individuals, including healthy people and thus, data are needed demonstrating that the known and potential benefits of the vaccine outweigh its known and potential risks. FDA published guidance for industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6]

2.6 Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. Data adequate to inform an assessment of the vaccine's benefits and risks, and thus support issuance of an EUA, would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry Development and Licensure of Vaccines to Prevent COVID-19 (June 2020) (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[6]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[7] From the perspective of vaccine efficacy, a 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.7 Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle requests for unblinding and crossover of placebo recipients to receive vaccine in the trial and loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

2.8 Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session to discuss, in general, the development, authorization, and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents
- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
  - Further evaluate safety, effectiveness and immune markers of protection
  - Evaluate the safety and effectiveness in specific populations.

On December 10, 2020, the VRBPAC met in open session to discuss the EUA request of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age older. Topics discussed at the meeting but not voted upon included Pfizer's plan for continuation of blinded, placebo-controlled follow-up in ongoing trials in the event that the vaccine is made available under EUA and gaps in plans for further evaluation of vaccine safety and effectiveness in populations that receive the Pfizer-BioNTech Vaccine under an EUA. The committee voted in favor of a determination that, based on the totality of scientific evidence

available, the benefits of the proposed vaccine outweigh its risks for use in individuals 16 years of age and older.

On December 17, 2020, the VRBPAC met to discuss the EUA request of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Committee members discussed but did not vote on whether the ongoing Phase 3 trial should be continued using a blinded cross-over design or an open-label design as proposed by Moderna. The committee suggested the conduct of additional studies to obtain data, including data on vaccine effectiveness in the elderly, immunogenicity in immunocompromised subpopulations, effectiveness of the vaccine following one dose, and the vaccine's duration of protection. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 18 years of age and older.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on February 26, 2021, to discuss and provide recommendations on whether based on the totality of scientific evidence available, the benefits of the Janssen Ad26.COV2.S vaccine outweigh its risks for use in individuals 18 years of age and older.

4. Janssen Ad26.COV2.S (COVID-19) Vaccine

4.1 Vaccine Composition, Dosing Regimen

The Janssen Ad26.COV2.S vaccine is a colorless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection. The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein in a stabilized conformation. The vaccine also contains the following inactive ingredients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin (HBCD), polysorbate 80, sodium chloride, sodium hydroxide, and hydrochloric acid.

The Ad26 vector expressing the SARS-CoV-2 S protein is grown in PER.C6® TetR Cell Line, in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is processed through several purification steps, formulated with inactive ingredients and filled into vials.

The Ad26.COV2.S vaccine is provided as a refrigerated suspension [stored at 2°C to 8°C (36°F to 46°F)] in a multi-dose vial containing 5 doses (0.5 mL each). The vials should be protected from light. Unpunctured vials may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. The vial should be discarded if the vaccine is not used within these times.

Ad26.COV2.S (5×10^{10} vp) is administered as a single intramuscular injection (0.5 mL dose).

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's guidance Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020). As such, FDA

has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2 Safety Experience of Ad26-based Vaccines

The Ad26.COV2.S (COVID-19) vaccine is based on the Ad26 vector platform. Clinical experience with the Ad26 platform consists of the Ad26.ZEBOV/MVA-BN-Filo Ebola vaccine regimen (approved by the European Medicines Agency on July 1, 2020) and investigational vaccines against Zika, filovirus, HIV, HPV, malaria, and respiratory syncytial virus. As of 31 December 2020, Ad26-based vaccines have been used to vaccinate 193,831 participants in clinical studies and vaccination programs. Overall, these vaccines have been shown to have an acceptable clinical safety profile to date.

4.3 Proposed Use Under EUA

The proposed use of the Ad26.COV2.S vaccine under an EUA is for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

5. FDA Review of Clinical Safety and Effectiveness Data

5.1 Overview of Clinical Studies

There are five ongoing clinical studies with Ad26.COV2.S, which are summarized in Table 1 below. All listed trials are randomized, double-blind, and placebo-controlled. Study VAC31518COV3001 (Study 3001) is a Phase 3 efficacy and safety study with a single-dose regimen and is the focus of the EUA review. Study 3009 is a Phase 3 efficacy and safety study with a 2-dose regimen than began in November 2020, for which only blinded safety data was available at the time of the EUA request. Study 2001 is a Phase 2a dose-ranging study exploring 4 dose levels and 1-dose and 2-dose regimens in adults and adolescents and will not be discussed in detail. Studies 1002 and 1001 are Phase 1 dose-ranging studies and will also not be discussed in detail. Summaries of the designs and results to date of Studies 1001, 1002, 2001, and 3009 may be found in Appendix A, page 60.

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

Study Number	Phase Type (Efficacy, Safety)	Participants Planned (N)	Test Product(s); Dosing Regimens	Study Status
3001	Phase 3 efficacy, safety	40,000 adults	Ad26.COV2.S $5x10^{10}$ vp 1-dose regimen	Enrollment complete
3009	Phase 3, efficacy, safety	30,000 adults	Ad26.COV2.S $5×10^{10}$ vp 2-dose regimen	Enrollment ongoing
2001	Phase 2a safety, immunogenicity	550 adults 660 adolescents	Ad26.COV2.S $1×10^{11}$ vp $5×10^{10}$ vp $2.5x10^{10}$ vp $1.25x10^{10}$ vp; 1-dose and 2-dose regimens	Enrollment of adults ongoing; enrollment of adolescents not started

Study Number	Phase Type (Efficacy, Safety)	Participants Planned (N)	Test Product(s); Dosing Regimens	Study Status
1002	Phase 1 safety, immunogenicity	250 adults	Ad26.COV2.S 5×10^{10} vp, 1×10^{11} vp; 2-dose regimen	Enrollment complete
1001	Phase 1/2a safety, immunogenicity	1045 adults	Ad26.COV2.S 5×10^{10} vp and 1×10^{11} vp; 1-dose and 2-dose regimens, with booster in 1 cohort	Enrollment complete

5.2 Study 3001

5.2.1 Design

Study 3001 is an ongoing randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of Ad26.COV2.S administered as a single dose in adults ≥18 years of age. A target of 40,000 adults were to be randomized 1:1 to receive intramuscular injections of either vaccine ($5x10^{10}$ vp) or placebo. At least 30% of the total study population was to consist of participants ≥60 years of age, and enrollment of participants 18 to 40 years of age was limited to approximately 20% of the total study population.

A staged enrollment strategy was specified in the protocol. Following acceptable safety and immunogenicity data from Study 1001 to support the dosing regimen, Study 3001 enrolled approximately 2000 participants 18 to 59 years of age without comorbidities (stage 1a). As no safety issues were identified during the Data Safety Monitoring Board's examination of safety data through Day 3 post-vaccination, participants 18 to 59 years with and without co-morbidities were enrolled (stage 1b). In parallel, approximately 2000 participants ≥60 years of age without comorbidities were enrolled (stage 2a) followed by a pause in vaccination for evaluation safety data through Day 3 post-vaccination prior to enrollment of ≥60-year-olds with and without comorbidities (stage 2b).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab. For the initial diagnosis of SARS-CoV-2 infection, FDA-authorized PCR tests were used, irrespective whether the test was performed locally at study sites or at the central laboratory (University of Washington [UW Virology laboratory]). Samples from locally diagnosed COVID-19 cases were to be sent to the central laboratory for confirmatory testing. Molecular confirmation of SARS-CoV-2 infection (using the Abbott Real Time SARS-CoV-2 RT-PCR assay) by the central laboratory was required to meet the co-primary and secondary efficacy endpoint case definitions.

The co-primary endpoints were efficacy of a single dose of vaccine to prevent centrally confirmed, moderate to severe/critical COVID-19 occurring (1) at least 14 days after vaccination and (2) at least 28 days after vaccination in study participants without evidence of prior SARS-CoV-2 infection at baseline. Evaluation of the co-primary endpoints was triggered by prespecified criteria:

1. The first 50% of participants have at least 2 months of follow-up after vaccination
2. At least 42 moderate to severe/critical cases of COVID-19 with onset at least 28 days after vaccination

3. At least 6 cases of COVID-19 among participants ≥60 years of age (onset ≥28 days after vaccination)
4. At least 5 severe/critical cases of COVID-19 in the placebo group (onset ≥28 days after vaccination) with a favorable vaccine-to-placebo split for both co-primary endpoints.

The protocol-specified "final analysis" will be performed when the last participant completes the visit 12 months post-vaccination or discontinues earlier. The end-of-study analysis will be performed when all participants have completed the visit 24 months post-vaccination or discontinued earlier. The expected duration of study participation is approximately 25 months.

Case Definitions

The case definition for moderate COVID-19 was a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal, throat, sputum, saliva) or other sample, **and** at any time during the course of observation:

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

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

OR

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

- Fever (≥38.0°C or ≥100.4°F)
- Heart rate ≥90 beats/minute
- Shaking chills or rigors
- Sore throat
- Cough
- Malaise as evidenced by loss of appetite, fatigue, physical weakness, and/or feeling unwell
- 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

The case definition for severe/critical COVID-19 was a RT-PCR or molecular test result from samples described above **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)
- 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 were adjudicated by a blinded clinical severity adjudication committee to determine if the case was severe/critical in their judgement.

Additionally, all cases meeting the moderate case definition and that included >3 signs and/or symptoms from the list of signs and symptoms were evaluated by the clinical severity adjudication committee to determine if the case was severe/critical in their judgement.

Primary Efficacy Endpoint

The originally specified primary endpoint was efficacy of the vaccine to prevent centrally confirmed, moderate to severe/critical COVID-19 occurring at least 14 days post-vaccination in SARS-CoV-2 seronegative adults (with "seronegative" defined as negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). Study protocol amendment 3 (December 14, 2020) added a co-primary endpoint counting COVID-19 cases from 28 days post-vaccination.

The primary analysis was based on the per-protocol set defined as those participants in the full analysis set (FAS) who received study vaccine, were seronegative at the time of vaccination, and had no major protocol deviations that were judged to possibly impact the efficacy of the vaccine.

A successful primary efficacy conclusion required two conditions:

1. Rejecting the null hypothesis H_0: VE ≤30% for each co-primary endpoint at a 2.5% one-sided significance level and a VE point estimate ≥50% for each co-primary endpoint;

   and

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

Both conditions 1 and 2 simultaneously had to be met for both co-primary endpoints at the same calendar timepoint. Exact Poisson regression was used to estimate VE and associated confidence intervals taking into account the follow-up time.

Secondary Efficacy Endpoints

Secondary endpoints included vaccine efficacy to prevent or vaccine impact on:

- Severe/critical COVID-19
- COVID-19 requiring medical intervention
- COVID-19-related death
- Any symptomatic COVID-19
- Asymptomatic COVID-19 as inferred through seroconversion
- COVID-19 per the FDA harmonized COVID-19 case definition

Vaccine efficacy of selected secondary endpoints was evaluated against a null hypothesis employing a lower limit VE >0% once hypothesis testing met the respective success criteria and data requirements for both co-primary endpoints. The case definition for mild COVID-19 (included in any symptomatic disease) and the FDA harmonized COVID-19 case definition may be found in Appendix B, page 62.

Evaluation of Safety

In Study 3001, the safety objective was evaluation of the safety of Ad26.COV2.S following vaccination. In a subset of participants (n=6736), local and systemic reactions were recorded from for 7 days following vaccination, and unsolicited AEs were collected from vaccination to day 28 after vaccination. In all participants, medically attended adverse events (MAAEs) were collected from vaccination to 6 months after vaccination, and MAAEs leading to study discontinuation and serious AEs (SAEs) were collected from vaccination to the end of the study.

Safety assessments included the following:

- Solicited local and systemic adverse reactions (ARs) that occurred during the 7 days following vaccination. Solicited ARs were recorded daily using eDiaries
- Unsolicited AEs observed or reported during the 28 days following vaccination. Unsolicited AEs are those not included in the protocol-defined solicited ARs
- Medically attended adverse events (MAAEs) from Day 1 through 6 months after vaccination
- MAAEs leading to discontinuation from study participation from Day 1 through 104 weeks following vaccinations
- SAEs from Day 1 through 104 weeks following vaccination or withdrawal from the study
- Vital sign measurements
- Physical examination findings
- Pregnancy and accompanying outcomes

AEs, including SAEs, associated with molecularly confirmed SARS-CoV-2 infection were removed from the analysis of adverse events.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. A stopping rule would be triggered if the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

Analysis Populations

For the purposes of analysis, the following populations are defined:

Table 2. Analysis Populations

Population	Description
Randomized	All participants who are randomized, regardless of the treatment status during the study.
Full analysis set	All randomized participants with a documented study vaccine administration. The FAS was used for all analyses of safety except solicited adverse reactions.
Per-protocol set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 at the time of vaccination and no major protocol deviations that were judged to possibly impact the efficacy of the vaccine.
Safety Subset	Subset of the full analysis set for the analysis of solicited and unsolicited AEs.

5.2.2 FDA Assessment of Phase 3 Follow-Up Duration

At the time of the primary analysis, the median follow-up duration for participants in the efficacy and safety analysis populations was 8 weeks after vaccination, which FDA considers to be

equivalent to 2 months and which meets the FDA expectation for follow-up after completion of the full vaccination regimen. Phased enrollment by age group and comorbidity risk resulted in slight differences in follow-up time between participants in these groups, with an approximately 2-week difference in the median follow up time between the first group enrolled (18-59 without comorbidities) and last group enrolled (60 years and older with comorbidities). Table 3 shows the median follow-up time by age and comorbidities in the FAS. Follow-up time in the per-protocol set is similar (data not shown).

Table 3. Participant Disposition by Age Group and Comorbidities, Full Analysis Set, Study 3001

Participant Group Follow-up	Ad26.COV2.S N=21895	Placebo N=21888	All Participants N=43783
18-59 overall	14564	14547	29111
Participants with at least 8 weeks follow-up	62.8%	63.1%	63.0%
Median follow-up after vaccination in days	61.0	61.0	61.0
18-59, no comorbidities	9332	9371	18703
Participants with at least 8 weeks follow-up	70.0%	69.9%	70.0%
Median follow-up after vaccination in days	64.0	64.0	64.0
18-59, with comorbidities	5232	5176	10408
Participants with at least 8 weeks follow-up	49.9%	50.8%	50.4%
Median follow-up after vaccination in days	56.0	57.0	57.0
≥60 years overall	7331	7341	14672
Participants with at least 8 weeks follow-up	38.2%	37.8%	38.0%
Median follow-up after vaccination in days	52.0	52.0	52.0
≥60 years, no comorbidities	3627	3595	7222
Participants with at least 8 weeks follow-up	47.6%	49.0%	48.3%
Median follow-up after vaccination in days	54.0	55.0	54.0
≥60 years, with comorbidities	3704	3746	7450
Participants with at least 8 weeks follow-up	29.0%	27.1%	28.0%
Median follow-up after vaccination in days	50.0	50.0	50.0

Source:Sponsor table TSIDS08

5.2.3 Participant Disposition and Inclusion in Analysis Populations

The tables below show the disposition of participants in the efficacy analysis population (Table 4) and safety analysis population (Table 5). The proportions of participants excluded from the

per-protocol set were balanced between treatment groups, with the majority of those excluded due to positive baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per-protocol set, 54.6% of vaccine recipients and 54.7% of placebo recipients completed at least 8 weeks follow-up after vaccination. As of the data cutoff date, 5.3% of participants in the vaccine group and 5.8% of participants in the placebo group in the per-protocol set were unblinded by request after they became eligible to receive an authorized COVID-19 vaccine under EUA. A slightly greater proportion of participants ≥60 years of age were unblinded (6.6%) compared to those 18 to 59 years of age (4.4%). The vast majority (93.0%) of participants who were unblinded were from US study sites. These participants were included in the per-protocol set until the time of the unblinding.

Table 4. Disposition[a], Efficacy Analysis Population, Study 3001

Disposition	Ad26.COV2.S n (%)	Placebo n (%)	Total n (%)
Randomized	22174	22151	44325
Vaccinated[a]	21895	21888	43783
Full analysis set	21895 (100.0)	21888 (100.0)	43783 (100.0)
Participants excluded from per-protocol set	2265 (10.3)	2197 (10.0)	4462 (10.2)
Positive SARS-CoV-2 status at time of vaccination based on serology and/or PCR	2233 (10.2)	2166 (9.9)	4399 (10.0)
Major protocol deviation evaluated to possibly impact efficacy	33 (0.2)	36 (0.2)	69 (0.2)
In/exclusion criteria	18 (0.1)	23 (0.1)	41 (0.1)
Received wrong treatment or incorrect dose	9 (<0.1)	11 (0.1)	20 (<0.1)
Received a disallowed concomitant medication	2 (<0.1)	2 (<0.1)	4 (<0.1)
Other	4 (<0.1)	1 (<0.1)	5 (<0.1)
Per-protocol set	19630 (89.7)	19691 (90.0)	39321 (89.8)
Participants with at least 8 weeks follow-up[b]	10715 (54.6)	10776 (54.7)	21491 (54.7)
Discontinued from study[b]	41 (0.2)	89 (0.5)	130 (0.3)
Reason for discontinuation[b]			
Withdrawal by participant	30 (0.2)	62 (0.3)	92 (0.2)
Death	1 (<0.1)	11 (0.1)	12 (<0.1)
Lost to follow-up	6 (<0.1)	4 (<0.1)	10 (<0.1)
Physician decision	2 (<0.1)	1 (<0.1)	3 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Other	2 (<0.1)	10 (0.1)	12 (<0.1)
Participants included in per-protocol set until treatment unblinding[b]	1046 (5.3)	1138 (5.8)	2184 (5.6)

Source: Sponsor table TSIDS02_A
[a] These values are denominators for the percentage calculations
[b] Based on the per protocol set

The table below summarizes the disposition of the safety analysis population. In the FAS, 54.6% of participants completed at least 8 weeks follow-up. The proportion of participants who discontinued from the study was 0.3% (n=145) across study groups, with a greater number in the placebo group (n=96) compared with the vaccine group (n=49). The most frequently

reported reason was withdrawal by participant. In the safety subset, almost all (99.9%) participants completed assessments through 29 days post-vaccination. As of the data cutoff date of January 22, 2021, in the FAS, 4.9% of participants in the vaccine group and 5.4% of participants in the placebo group were unblinded due to request by participant after the participant became eligible to receive an authorized COVID-19 vaccine under EUA.

Table 5. Disposition, Safety Analysis Population, Study 3001

Disposition	Ad26.COV2.S n (%)	Placebo n (%)	Total n (%)
Randomized	22174	22151	44325
Vaccinated[a]	21895	21888	43783
Vaccinated with incorrect vaccine	6	5	11
Full analysis set	21895 (100.0)	21888 (100.0)	43783 (100.0)
Participants with at least 8 weeks follow-up	11948 (54.6)	11955 (54.6)	23903 (54.6)
Participants unblinded to treatment	1080 (4.9)	1177 (5.4)	2257 (5.2)
Discontinued from study	49 (0.2%)	96 (0.4%)	145 (0.3)
Reason for discontinuation			
Withdrawal by participant	35 (0.2)	66 (0.3)	101 (0.2)
Death	2 (<0.1)	12 (0.1)	14 (<0.1)
Lost to follow-up	6 (<0.1)	5 (<0.1)	11 (<0.1)
Physician decision	2 (<0.1)	1 (<0.1)	3 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Other	4 (<0.1)	11 (0.1)	15 (<0.1)
Safety subset	3356 (15.3)	3380 (15.4)	6736 (15.4)
Completed post-vaccination (Day 1-29)[b]	3354 (99.9)	3376 (99.9)	6730 (99.9)

[a] These values are denominators for the percentage calculations
[b] Percentage based on Safety subset

5.2.4 Demographics and Other Baseline Characteristics

In the per-protocol set, 44.5% of participants were female and 20.4% were ≥65 years of age. Overall, 62.1% of participants were white, 17.2% Black or African American, 8.3% American Indian or Alaska Native, 3.5% Asian, 0.3% Native Hawaiian or other Pacific Islander, and 5.4% multiracial; 45.1% of participants were Hispanic/Latino. At least one comorbidity was present for 39.9% of participants. Geographically, 46.7% of subjects participated in the United States, 17.3% in Brazil, 12.7% in South Africa, and the remaining 23.3% in 5 different countries in Latin America. Baseline demographics in US participants included in the study were similar to that of the global demographics, with the exception of lower percentages of subjects who were American Indian or Alaska Native (1.0%) and subjects who identified as Hispanic or Latino (14.2%). There was a similar distribution of demographic characteristics between the treatment groups.

Table 6. Demographic Characteristics, Per-Protocol Set, Study 3001

Subgroup	Ad26.COV2.S	Placebo	All Participants
Per-protocol set	**19630**	**19691**	**39321**
Age (years)			
Mean (SD)	51.1 (15.0)	51.2 (15.0)	51.1 (15.0)
Median	52.0	53.0	53.0
Range	(18, 100)	(18, 94)	(18, 100)

Subgroup	Ad26.COV2.S	Placebo	All Participants
Per-protocol set	**19630**	**19691**	**39321**
Age group (years)			
18-59	12830 (65.4%)	12881 (65.4%)	25711 (65.4%)
≥60	6800 (34.6%)	6810 (34.6%)	13610 (34.6%)
≥65	3984 (20.3%)	4018 (20.4%)	8002 (20.4%)
≥75	755 (3.8%)	693 (3.5%)	1448 (3.7%)
Sex			
Female	8702 (44.3%)	8777 (44.6%)	17479 (44.5%)
Male	10924 (55.6%)	10910 (55.4%)	21834 (55.5%)
Undifferentiated	2 (<0.1%)	4 (<0.1%)	6 (<0.1%)
Unknown	2 (<0.1%)	0	2 (<0.1%)
Race			
American Indian or Alaska Native	1643 (8.4%)	1628 (8.3%)	3271 (8.3%)
Asian	720 (3.7%)	663 (3.4%)	1383 (3.5%)
Black or African American	3374 (17.2%)	3390 (17.2%)	6764 (17.2%)
Native Hawaiian or other Pacific Islander	54 (0.3%)	45 (0.2%)	99 (0.3%)
White	12200 (62.1%)	12216 (62.0%)	24416 (62.1%)
Multiple	1036 (5.3%)	1087 (5.5%)	2123 (5.4%)
Unknown	603 (3.1%)	662 (3.4%)	1265 (3.2%)
Ethnicity			
Hispanic or Latino	8793 (44.8%)	8936 (45.4%)	17729 (45.1%)
Not Hispanic or Latino	10344 (52.7%)	10259 (52.1%)	20603 (52.4%)
Unknown	493 (2.5%)	496 (2.5%)	989 (2.5%)
Region and Country			
Latin America	7967 (40.6%)	8014 (40.7%)	15981 (40.6%)
Brazil	3399 (17.3%)	3390 (17.2%)	6789 (17.3%)
Chile	531 (2.7%)	540 (2.7%)	1071 (2.7%)
Argentina	1402 (7.1%)	1414 (7.2%)	2816 (7.2%)
Colombia	1858 (9.5%)	1869 (9.5%)	3727 (9.5%)
Peru	571 (2.9%)	581 (3.0%)	1152 (2.9%)
Mexico	206 (1.0%)	220 (1.1%)	426 (1.1%)
Northern America	9185 (46.8%)	9171 (46.6%)	18356 (46.7%)
United States	9185 (46.8%)	9171 (46.6%)	18356 (46.7%)
Southern Africa	2478 (12.6%)	2506 (12.7%)	4984 (12.7%)
South Africa	2478 (12.6%)	2506 (12.7%)	4984 (12.7%)
Presence of baseline comorbidity			
One or more	7830 (39.9%)	7867 (40.0%)	15697 (39.9%)
None	11800 (60.1%)	11824 (60.0%)	23624 (60.1%)

Source: Sponsor table TSIDEM01_A

The demographic characteristics among vaccine and placebo participants in the FAS were similar. There were no significant imbalances in demographic or other baseline characteristics between the per-protocol set and FAS. Overall, 9.6% of vaccinated participants in the study had evidence of previous infection with SARS-CoV-2 at baseline, as assessed by serology prior to vaccination.

Table 7. Demographic Characteristics, Full Analysis Set, Study 3001

Subgroup	Ad26.COV2.S	Placebo	All Participants
Full analysis set	**21895**	**21888**	**43783**
Age (years)			
Mean (SD)	50.7 (15.1)	50.7 (15.0)	50.7 (15.1)
Median	52.0	52.0	52.0
Range	(18, 100)	(18, 94)	(18, 100)
Age group			
18-59	14564 (66.5%)	14547 (66.5%)	29111 (66.5%)
≥60	7331 (33.5%)	7341 (33.5%)	14672 (33.5%)
≥65	4259 (19.5%)	4302 (19.7%)	8561 (19.6%)
≥75	809 (3.7%)	732 (3.3%)	1541 (3.5%)
Sex			
Female	9820 (44.9%)	9902 (45.2%)	19722 (45.0%)
Male	12071 (55.1%)	11982 (54.7%)	24053 (54.9%)
Undifferentiated	2 (<0.1%)	4 (<0.1%)	6 (<0.1%)
Unknown	2 (<0.1%)	0	2 (<0.1%)
Race			
American Indian or Alaska Native	2083 (9.5%)	2060 (9.4%)	4143 (9.5%)
Asian	743 (3.4%)	687 (3.1%)	1430 (3.3%)
Black or African American	4251 (19.4%)	4264 (19.5%)	8515 (19.4%)
Native Hawaiian or other Pacific Islander	58 (0.3%)	48 (0.2%)	106 (0.2%)
White	12858 (58.7%)	12838 (58.7%)	25696 (58.7%)
Multiple	1204 (5.5%)	1245 (5.7%)	2449 (5.6%)
Unknown	308 (1.4%)	315 (1.4%)	623 (1.4%)
Ethnicity			
Hispanic or Latino	9874 (45.1%)	9963 (45.5%)	19837 (45.3%)
Not Hispanic or Latino	11472 (52.4%)	11362 (51.9%)	22834 (52.2%)
Unknown	197 (0.9%)	199 (0.9%)	396 (0.9%)
Region and country			
Latin America	8954 (40.9%)	8951 (40.9%)	17905 (40.9%)
Argentina	1498 (6.8%)	1498 (6.8%)	2996 (6.8%)
Brazil	3644 (16.6%)	3634 (16.6%)	7278 (16.6%)
Chile	563 (2.6%)	570 (2.6%)	1133 (2.6%)
Colombia	2125 (9.7%)	2123 (9.7%)	4248 (9.7%)
Mexico	238 (1.1%)	241 (1.1%)	479 (1.1%)
Peru	886 (4.0%)	885 (4.0%)	1771 (4.0%)
Northern America	9655 (44.1%)	9647 (44.1%)	19302 (44.1%)
United States	9655 (44.1%)	9647 (44.1%)	19302 (44.1%)
Southern Africa	3286 (15.0%)	3290 (15.0%)	6576 (15.0%)
South Africa	3286 (15.0%)	3290 (15.0%)	6576 (15.0%)
SARS-CoV-2 serostatus status at baseline			
Positive	2151 (9.8%)	2066 (9.4%)	4217 (9.6%)
Negative	19104 (87.3%)	19191 (87.7%)	38295 (87.5%)
Missing	640 (2.9%)	631 (2.9%)	1271 (2.9%)
Presence of baseline comorbidity			
One or more	8936 (40.8%)	8922 (40.8%)	17858 (40.8%)
None	12959 (59.2%)	12966 (59.2%)	25925 (59.2%)

Source: Sponsor table TSIDEM01_B

The following table provides the proportions of participants with one or more comorbidities associated with an increased risk of progression to severe COVID-19. In the FAS, 40.8% of participants had one or more comorbidities at baseline. The most common comorbidities were obesity (28.5%) and hypertension (10.3%). The study also included participants who were HIV positive (2.8%). The proportions of individuals with comorbidities were similar between the vaccine and placebo groups and between the FAS and per-protocol set.

Table 8. Participants With Comorbidities, Full Analysis Set, Study 3001

Baseline Comorbidity Category	Ad26.COV2.S (N=21895) n (%)	Placebo (N=21888) n (%)	Total (N=43783) n (%)
No comorbidity	12959 (59.2)	12966 (59.2)	25925 (59.2)
With one or more comorbidity	8936 (40.8)	8922 (40.8)	17858 (40.8)
Asthma	262 (1.2)	300 (1.4)	562 (1.3)
Cancer	112 (0.5)	114 (0.5)	226 (0.5)
Cerebrovascular disease	78 (0.4)	80 (0.4)	158 (0.4)
Cystic fibrosis	1 (<0.1)	3 (<0.1)	4 (<0.1)
Chronic kidney disease	112 (0.5)	118 (0.5)	230 (0.5)
COPD	231 (1.1)	206 (0.9)	437 (1.0)
Serious heart conditions	497 (2.3)	511 (2.3)	1008 (2.3)
HIV infection[a]	601 (2.7)	617 (2.8)	1218 (2.8)
Hypertension[b]	2225 (10.2)	2296 (10.5)	4521 (10.3)
Immunocompromised state from blood transplant	43 (0.2)	36 (0.2)	79 (0.2)
Immunocompromised state from organ transplant	7 (<0.1)	3 (<0.1)	10 (<0.1)
Liver disease	103 (0.5)	103 (0.5)	206 (0.5)
Neurologic conditions	82 (0.4)	125 (0.6)	207 (0.5)
Obesity[c]	6277 (28.7)	6215 (28.4)	12492 (28.5)
Pulmonary fibrosis	10 (<0.1)	9 (<0.1)	19 (<0.1)
Sickle cell disease	13 (0.1)	5 (<0.1)	18 (<0.1)
Type 1 diabetes mellitus	105 (0.5)	90 (0.4)	195 (0.4)
Type 2 diabetes mellitus	1600 (7.3)	1594 (7.3)	3194 (7.3)
Thalassemia	16 (0.1)	30 (0.1)	46 (0.1)

Source: Sponsor table TSIDEM01_B
[a] HIV status not collected for participants with no-comorbidities and no medical history of HIV
[b] >150 mm Hg systolic and/or >95 mm Hg diastolic
[c] body mass index >30 kg/m^2

Subjects in the safety subset were enrolled from 45 sites in 3 Tier 1 countries (US, Brazil and South Africa). The Tier 1 countries were selected based on rapid start-up capacity and projected incidence rates for COVID-19 that would allow for rapid efficacy signal detection. At the site level, investigators questioned participants on their willingness to be part of the safety subset. Selection and randomization of the participants was then completed through a web-based randomization system. In safety subset, 48.3% of participants were female, and 23.0% were ≥65 years of age, which is similar to the FAS. A larger percentage of participants in the safety subset were white (83.4%) compared to the FAS (58.7%). Geographically, the safety subset was limited to participants in the United States (51.4%), South Africa (10.2%), and Brazil (38.5%). Fewer participants in the safety subset compared to the FAS were seropositive at baseline (4.5% versus 9.6%) and had a least one comorbidity (34.1% versus 40.8%).

Table 9. Demographic Characteristics, Safety Subset, Study 3001

Subgroup	Ad26.COV2.S	Placebo	Total
Safety Subset	**3356**	**3380**	**6736**
Age (years)			
Mean (SD)	51.4 (15.9)	51.1 (16.1)	51.2 (16.0)
Median	54.0	54.0	54.0
Range	(18, 90)	(18, 91)	(18, 91)
Age group (years)			
18-59	2036 (60.7%)	2049 (60.6%)	4085 (60.6%)
≥60	1320 (39.3%)	1331 (39.4%)	2651 (39.4%)
≥65	763 (22.7%)	786 (23.3%)	1549 (23.0%)
≥75	150 (4.5%)	138 (4.1%)	288 (4.3%)
Sex			
Female	1637 (48.8%)	1615 (47.8%)	3252 (48.3%)
Male	1719 (51.2%)	1765 (52.2%)	3484 (51.7%)
Undifferentiated	0	0	0
Unknown	0	0	0
Race			
American Indian or Alaska Native	9 (0.3%)	9 (0.3%)	18 (0.3%)
Asian	114 (3.4%)	105 (3.1%)	219 (3.3%)
Black or African American	267 (8.0%)	260 (7.7%)	527 (7.8%)
Native Hawaiian or other Pacific Islander	9 (0.3%)	10 (0.3%)	19 (0.3%)
White	2798 (83.4%)	2823 (83.5%)	5621 (83.4%)
Multiple	97 (2.9%)	112 (3.3%)	209 (3.1%)
Unknown	20 (0.6%)	17 (0.5%)	37 (0.5%)
Ethnicity			
Hispanic or Latino	1284 (38.3%)	1287 (38.1%)	2571 (38.2%)
Not Hispanic or Latino	2024 (60.3%)	2038 (60.3%)	4062 (60.3%)
Unknown	12 (0.4%)	14 (0.4%)	26 (0.4%)
Region and country			
Latin America	1291 (38.5%)	1299 (38.4%)	2590 (38.5%)
Argentina	0	0	0
Brazil	1291 (38.5%)	1299 (38.4%)	2590 (38.5%)
Chile	0	0	0
Colombia	0	0	0
Mexico	0	0	0
Peru	0	0	0
Northern America	1727 (51.5%)	1735 (51.3%)	3462 (51.4%)
United States	1727 (51.5%)	1735 (51.3%)	3462 (51.4%)
Southern Africa	338 (10.1%)	346 (10.2%)	684 (10.2%)
South Africa	338 (10.1%)	346 (10.2%)	684 (10.2%)
SARS-CoV-2 serostatus status at baseline			
Positive	154 (4.6%)	147 (4.3%)	301 (4.5%)
Negative	3117 (92.9%)	3129 (92.6%)	6246 (92.7%)
Missing	85 (2.5%)	104 (3.1%)	189 (2.8%)
Presence of baseline comorbidity			
One or more	1135 (33.8%)	1164 (34.4%)	2299 (34.1%)
None	2221 (66.2%)	2216 (65.6%)	4437 (65.9%)

Source: Sponsor table TSIDEM01_D

5.2.5 Vaccine Efficacy

Primary Efficacy Analysis

The primary efficacy analysis was based on the per-protocol set, which consisted of all vaccinated participants who were SARS-CoV-2 seronegative at time of vaccination and who had no major protocol deviations. The co-primary efficacy endpoints were vaccine efficacy (VE) in preventing protocol-defined moderate to severe/critical COVID-19, confirmed by the central laboratory, occurring at least 14 days and at least 28 days after vaccination, respectively. The primary efficacy success criterion would be met if the null hypothesis of VE ≤30% is rejected and the VE point estimate is ≥50% for both co-primary endpoints at the primary analysis. As shown in Table 10, in participants ≥18 years of age, VE against moderate to severe/critical COVID-19 with onset at least 14 days after vaccination was 66.9% (a lower bound of the 95% CI of 59.03), and VE against moderate to severe/critical COVID-19 with onset at least 28 days after vaccination was 66.1% (a lower bound of 95% CI of 55.01), which together met the pre-specified success criteria. Vaccine efficacy was similar between the two age groups of participants 18 to 59 and ≥60 years of age.

Table 10. Vaccine Efficacy Against Centrally Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 and at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Co-primary Endpoint Subgroup	**Ad26.COV2.S Cases (N)[a] Person-yrs[b]**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**
All participants	116 (19514) 3116.6	348 (19544) 3096.1	66.9% (59.0, 73.4)	66 (19306) 3102.0	193 (19178) 3070.7	66.1% (55.0, 74.8)
Age 18-59 years	95 (12750) 2106.8	260 (12782) 2095.0	63.7% (53.9, 71.6)	52 (12617) 2097.6	152 (12527) 2077.0	66.1% (53.3, 75.8)
Age ≥60 years	21 (6764) 1009.8	88 (6762) 1001.2	76.3% (61.6, 86.0)	14 (6689) 1004.4	41(6651) 993.6	66.2% (36.7, 83.0)

Source: Sponsor tables GEFPE02_A and GEFPE02_C
[a] N=Total number of participants at risk per category
[b] Person-years include time from vaccination to the onset of moderate to severe/critical COVID-19, discontinuation from study, major protocol deviation, unblinding to receive alternative vaccine, or data cutoff, whichever comes first.

Due to the high incidence rate of COVID-19 during the study, not all positive PCR tests had been confirmed by the central laboratory at the time of data cutoff. Of 682 primary endpoint cases with positive PCR from any lab accrued at the time of the data cutoff date, 464 were centrally confirmed. The statistical analysis plan specified that the primary and secondary endpoints would be based on centrally confirmed COVID-19, and thus only centrally confirmed cases were included in analyses of vaccine efficacy. For the subgroup analyses for the primary and secondary endpoints, positive PCR results from any source were used to increase the number of cases and the precision of the estimate. At the time of the data cutoff, there was high concordance between all local and central laboratory PCR results (90.3%). Evaluation of the primary efficacy endpoint including non-centrally-confirmed cases yielded results similar to those reported above (66.3% and 65.5% for onset at least 14 days and at least 28 days after vaccination, respectively). On February 12, the Sponsor submitted an update on centrally confirmed cases as an amendment to the EUA request; based on cases accrued by the time of the data cutoff and analyzed by the central laboratory by February 8, 582 primary endpoint cases were centrally confirmed. Vaccine efficacy based on this updated dataset was similar to that reported above (67.4% and 66.2% for onset at least 14 days and at least 28 days after vaccination, respectively). The high rate of concordance between local and central lab PCR tests and similar co-primary analysis results regardless of inclusion or exclusion of non-centrally

confirmed cases support the inclusion of cases awaiting central laboratory confirmation in subgroup analyses to increase their robustness and improve interpretability.

The demographics of participants with moderate to severe/critical COVID-19, including non-centrally confirmed cases, with onset at least 14 days after vaccination are displayed below. The majority of COVID-19 cases were among participants in the United States, South Africa, and Brazil. Study participants with comorbidities were not over-represented among COVID-19 cases as compared to the overall study population.

Table 11. Demographic Characteristics of Participants With Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 days After Vaccination, Per-Protocol Set

Subgroup	Ad26.COV2.S N (%)	Placebo N (%)	All Participants N (%)
All participants	**173**	**509**	**682**
Age group (years)			
18-59	137 (79.2%)	389 (76.4%)	526 (77.1%)
≥60	36 (20.8%)	120 (23.6%)	156 (22.9%)
Sex			
Female	88 (50.9%)	240 (47.2%)	328 (48.1%)
Male	85 (49.1%)	269 (52.9%)	354 (51.9%)
Race			
American Indian or Alaska Native	21 (12.1%)	41 (8.1%)	62 (9.1%)
Asian	6 (3.5%)	12 (2.4%)	18 (2.6%)
Black or African American	37 (21.4%)	101 (19.8%)	138 (20.2%)
Native Hawaiian or other Pacific Islander	1 (0.6%)	0 (0.0%)	1 (0.2%)
White	94 (54.3%)	288 (56.6%)	382 (56.0%)
Multiple	10 (5.8%)	48 (9.4%)	58 (8.5%)
Unknown/ not reported	4 (2.3%)	19 (3.7%)	23 (3.4%)
Ethnicity			
Hispanic or Latino	81 (46.8%)	237 (46.6%)	318 (46.6%)
Not Hispanic or Latino	88 (50.9%)	257 (50.5%)	345 (50.6%)
Unknown/ not reported	4 (2.3%)	15 (3.0%)	19 (2.8%)
Country			
United States	51 (29.5%)	196 (38.5%)	247 (36.2%)
South Africa	43 (24.9%)	90 (17.7%)	133 (19.5%)
Brazil	39 (22.5%)	114 (22.4%)	153 (22.4%)
Colombia	22 (12.7%)	62 (12.2%)	84 (12.3%)
Argentina	8 (4.6%)	30 (5.9%)	38 (5.6%)
Peru	7 (4.1%)	13 (2.6%)	20 (2.9%)
Chile	2 (1.2%)	4 (0.8%)	6 (0.9%)
Mexico	1 (0.6%)	0 (0.0%)	1 (0.2%)

Subgroup	Ad26.COV2.S N (%)	Placebo N (%)	All Participants N (%)
All participants	**173**	**509**	**682**
Presence of baseline comorbidity			
None	103 (59.5%)	315 (61. 9%)	418 (61.3%)
One or more	70 (40.5%)	194 (38.1%)	264 (38.7%)
Obesity	51 (29.5%)	151 (29.7%)	202 (29.6%)
Hypertension	14 (8.1%)	38 (7.5%)	52 (7.6%)
Type 2 diabetes mellitus	15 (8.7%)	32 (6.3%)	47 (6.9%)
Serious heart condition	3 (1.7%)	13 (2.6%)	16 (2.4%)
Asthma	1 (0.6%)	9 (1.8%)	10 (1.5%)
HIV infection	5 (2.9%)	5 (1.0%)	10 (1.5%)
COPD	1 (0.6%)	5 (1.0%)	6 (0.9%)
Liver disease	1 (0.6%)	2 (0.4%)	3 (0.4%)
Cancer	0 (0.0%)	2 (0.4%)	2 (0.3%)
Immunocompromised from blood transplant	2 (1.2%)	0 (0.0%)	2 (0.3%)
Neurologic conditions	0 (0.0%)	1 (0.2%)	1 (0.2%)

Source: Sponsor response to IR 17

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the co-primary efficacy endpoints provide additional information on the applicability of these results across the general population. For the subgroup analyses, cases with any positive PCR, including those still awaiting confirmation by the central laboratory, were included. In general, VE among the subgroups are similar to the VE in the overall study population. The VE results for subgroups with small numbers of participants (e.g., participants ≥75 years of age, certain racial subgroups) have limited interpretability but are displayed for completeness.

Table 12. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 or at Least 28 Days After Vaccination, by Demographic Characteristics, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Sex						
Male	85 (10861) 1739.0	269 (10832) 1715.9	68.8% (60.1, 75.9)	54 (10764) 1732.4	176 (10649) 1704.2	69.8% (58.9, 78.2)
Female	88 (8649) 1374.2	240 (8708) 1372.6	63.4% (53.1, 71.7)	59 (8538) 1367.1	148 (8525) 1361.1	60.3% (46.0, 71.2)
Age group (yrs)						
18-64	157 (15544) 2527.8	441 (15552) 2504.8	64.7% (57.6, 70.8)	101 (15378) 2517.1	286 (15253) 2485.9	65.1% (56.1, 72.5)
≥65	16 (3970) 586.1	68 (3992) 584.3	76.5% (59.1, 87.3)	12 (3928) 583.1	38 (3925) 580.0	68.6% (38.6, 85.1)
≥75	1 (751) 107.3	9 (690) 99.1	89.7% (26.0, 99.8)	0 (740) 106.4	4 (673) 98.0	
Race						
Amer. Indian/ Alaskan	21 (1634) 279.0	41 (1621) 275.4	49.4% (12.4, 71.6)	18 (1628) 278.4	26 (1604) 274.4	31.7% (-29.4, 64.8)

Subgroup	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Asian	6 (714) 99.5	12 (649) 90.6	54.4% (-31.1, 86.0)	2 (689) 97.9	7 (626) 89.1	74.0% (-36.5, 97.4)
Black or African Amer.	37 (3362) 495.7	101 (3361) 491.4	63.7% (46.6, 75.8)	21 (3330) 493.7	66 (3300) 487.3	68.6% (48.0, 81.8)
Native Hawaiian/ Other	1 (54) 8.0	0 (44) 6.6		1 (54) 8.0	0 (43) 6.6	
White	94 (12123) 1975.4	288 (12133) 1958.3	67.6% (59.0, 74.6)	64 (11994) 1967.0	187 (11912) 1944.4	66.2% (54.8, 74.9)
Multiple	10 (1028) 166.6	48 (1080) 170.8	78.6% (57.3, 90.4)	4 (1018) 166.0	28 (1055) 169.2	85.4% (58.4, 96.3)
Ethnicity						
Hispanic/ Latino	81 (8733) 1418.6	237 (8869) 1429.3	65.6% (55.5, 73.6)	59 (8688) 1415.7	153 (8741) 1421.4	61.3% (47.4, 71.8)
Not Hispanic/ Latino	88 (10289) 1620.3	257 (10184) 1587.7	66.4% (57.1, 74.0)	52 (10131) 1610.1	163 (9957) 1573.1	68.8% (57.2, 77.6)
Region						
Northern America (U.S.)	51 (9119) 1414.0	196 (9086) 1391.3	74.4% (65.0, 81.6)	32 (8958) 1403.4	112 (8835) 1375.6	72.0% (58.2, 81.7)
Southern Africa (South Africa)	43 (2473) 377.6	90 (2496) 379.2	52.0% (30.3, 67.4)	23 (2449) 376.1	64 (2463) 376.9	64% (41.2, 78.7)
Latin America	79 (7922) 1322.2	223 (7962) 1318.5	64.7% (54.1, 73.0)	58 (7899) 1320.8	148 (7880) 1313.3	61.0% (46.9, 71.8)

N=Total number of participants at risk per category
[a] If fewer than 6 cases are observed for an endpoint then the VE is not shown.
Source: Sponsor tables GEFPE09A, GEFPE09C

Additional subgroup analyses were conducted to evaluate vaccine efficacy by risk factor for severe COVID-19. Vaccine efficacy against moderate to severe/critical COVID-19 with onset at least 28 days after vaccination was lower for individuals with comorbid conditions than for those without such conditions, especially in the subgroup of participants ≥60 years of age. However, the confidence intervals are wide, and the uncertainty of the point estimate is large, as shown in Table 13. The wide confidence intervals for the ≥28 days endpoint are attributable to lower numbers of cases due to the relatively shorter follow up duration (median of approximately 7 weeks) and with a greater proportion of participants in this subgroup who were unblinded (6.0% compared to 4.4% for 18-59 years cohort overall) due to eligibility for authorized COVID-19 vaccine under EUA, smaller number of participants, and lower incidence of COVID-19 in the cohort of those ≥60 years with comorbidities. For this and several other subgroups, the VE estimate increased and the confidence interval narrowed as the number of cases included in the analysis increased (with inclusion of non-centrally confirmed cases and with cases starting after 14 days), indicating that the apparent lower VE estimates in certain analyses potentially reflect imprecision associated with smaller numbers of cases. For a majority of individual comorbid conditions, interpretation of the results is limited by small sample size and low incidence of

COVID-19. However, for subgroups with higher incidence of COVID-19, such as participants with obesity, the VE was similar to the VE estimate in the overall study population.

Table 13. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 or at Least 28 Days After Vaccination, by Risk Factors for Severe COVID-19, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Comorbidity, presence						
Yes	70 (7777) 1138.8	194 (7798) 1130.9	64.2% (52.7, 73.1)	44 (7684) 1133.0	105 (7626) 1120.0	58.6% (40.6, 71.6)
No	103 (11737) 1975.1	315 (11746) 1958.2	67.6% (59.4, 74.3)	69 (11622) 1967.3	219 (11552) 1945.9	68.8% (59.0, 76.6)
Age group and comorbidity presence						
18-59, no	89 (8346) 1433.5	258 (8411) 1428.2	65.6% (56.1, 73.3)	58 (8267) 1428.2	180 (8254) 1418.3	68.0% (56.8, 76.6)
18-59, yes	48 (4404) 671.5	131 (4371) 661.0	63.9% (49.4, 74.7)	29 (4350) 668.1	79 (4273) 654.8	64.0% (44.3, 77.3)
≥60, no	14 (3391) 541.6	57 (3335) 530.0	76.0% (56.3, 87.6)	11 (3355) 539.0	39 (3298) 527.6	72.4% (45.0, 87.3)
≥60, yes	22 (3373) 467.4	63 (3427) 469.9	64.9% (42.2, 79.4)	15 (3334) 464.9	26 (3353) 465.2	42.3% (-13.1, 71.6)
Comorbidity, type[b]						
Asthma	1 (238) 34.3	9 (278) 39.5	87.2% (7.6, 99.7)	0 (235) 34.1	4 (270) 38.9	
Cancer	0 (104) 14.2	2 (108) 15.0		0 (102) 14.1	0 (105) 14.8	
Chronic kidney disease	0 (106) 15.1	1 (109) 15.3		0 (102) 14.8	0 (106) 15.1	
COPD	1 (213) 30.2	5 (195) 28.0	81.5% (-65.2, 99.6)	1 (211) 30.1	3 (192) 27.8	
Serious heart conditions	3 (460) 65.3	13 (487) 67.7	76.1% (12.9, 95.6)	1 (455) 64.9	5 (472) 66.8	79.4% (-83.7, 99.6)
HIV infection	5 (467) 69.1	5 (498) 72.4	-4.8% (-355.2, 75.9)	2 (461) 68.7	4 (493) 72.2	47.5% (-266.0, 95.3)
Hypertension	14 (1999) 283.3	38 (2019) 282.8	63.2% (30.6, 81.6)	11 (1978) 281.9	17 (1977) 280.2	35.7% (-45.6, 72.8)
Immuno-compromised from blood transplant	2 (38) 4.9	0 (33) 4.6		1 (35) 4.7	0 (32) 4.5	
Liver disease	1 (97) 14.5	2 (100) 14.7		1 (96) 14.4	0 (98) 14.6	
Neurologic conditions	0 (77) 11.1	1 (115) 16.5		0 (77) 11.1	1 (114) 16.5	
Obesity	51 (5383) 794.1	151 (5352) 780.3	66.8% (54.1, 76.3)	30 (5318) 790.0	86 (5223) 772.0	65.9% (47.8, 78.3)

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Type 2 diabetes mellitus	15 (1399) 198.7	32 (1410) 199.5	52.9% (10.5, 76.3)	10 (1380) 197.5	13 (1378) 197.7	23.0% (-90.1, 69.8)

Source: Sponsor tables GEFPE09A, GEFPE09C
N=Total number of participants at risk per category
[a] If fewer than 6 cases are observed for an endpoint then the VE is not shown.
[b] Results not shown for comorbidities which did not have any cases in either arm for either of the two time periods

Among the 4,156 participants with positive baseline SARS-CoV-2 status who would have otherwise fulfilled the criteria for the Per Protocol Set, there were 7 moderate to severe/critical COVID-19 cases which occurred at least 14 days post-vaccination (3 in vaccine group, 4 in placebo group), of which 3 cases occurred at least 28 days post-vaccination (1 in vaccine group, 2 in placebo group). One case, in a participant in the vaccine group, was assessed as severe. Of the 7 cases, only one case was centrally confirmed at the time of the data cutoff. There is insufficient data at this time to evaluate vaccine efficacy in previously infected individuals.

Table 14. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 or at Least 28 Days After Vaccination, by Baseline SARS-CoV-2 Status[a], Per Protocol Set

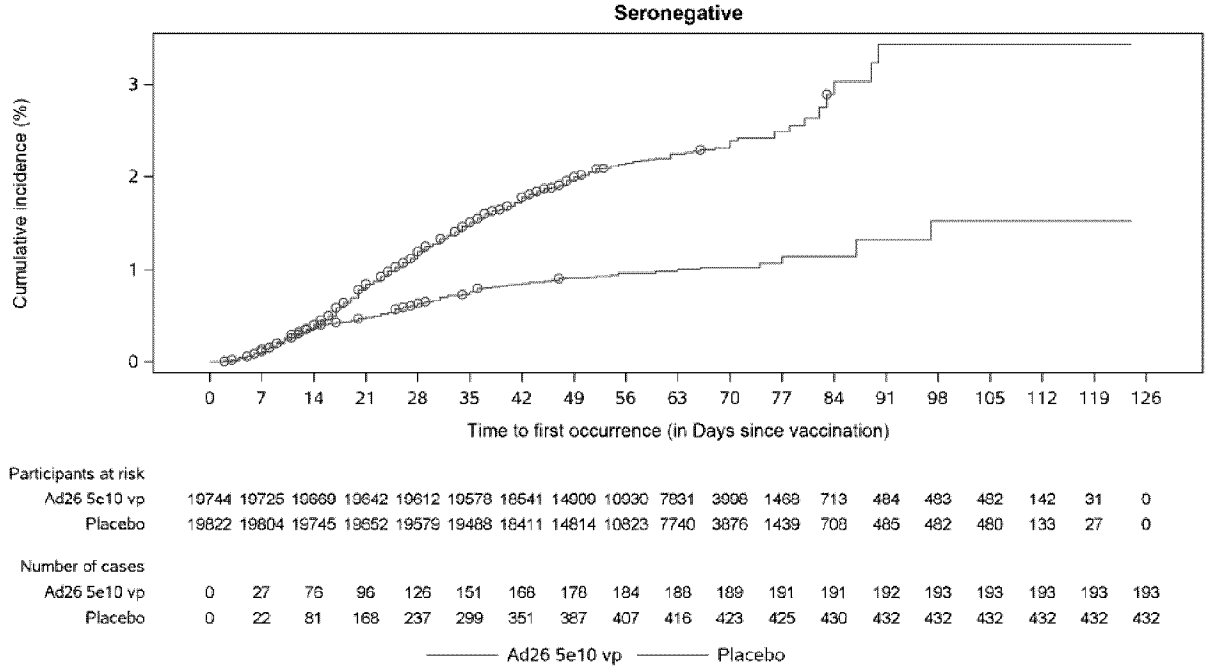
	Onset at Least 14 Days			Onset at Least 28 Days		
Baseline SARS-CoV-2 Serostatus[a]	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[b] (95% CI)
Regardless of baseline SARS-CoV-2 status	176 (21636) 3450.2	513 (21574) 3409.8	66.1% (59.7, 71.6)	114 (21424) 3436.3	326 (21199) 3385.9	65.5% (57.2, 72.4)
Positive	3 (2122) 336.3	4 (2030) 320.8	28.5% (-322.8, 89.5)	1 (2118) 336.1	2 (2021) 320.0	
Negative	173 (19514) 3113.9	509 (19544) 3089.1	66.3% (59.9, 71.8)	113 (19306) 3100.3	324 (19178) 3065.9	65.5% (57.2, 72.4)

Source: Sponsor tables GEFPE07A, GEFPE07C
N=Total number of participants at risk per category
[a] Based on serological test at baseline
[b] If fewer than 6 cases are observed for an endpoint then the VE is not shown

Cumulative Incidence Curves –Primary Efficacy Analysis

Cumulative incidence of moderate to severe/critical COVID-19 in the FAS was similar in both the vaccine and placebo groups until around Day 14, following which the curves diverge, with more cases accumulating in the placebo group than the vaccine group.

Figure 1. Cumulative Incidence Curve of Centrally Confirmed Moderate to Severe/Critical COVID-19 Cases With Onset at Least 1 Day After Vaccination, Full Analysis Set



Secondary Efficacy Analyses

Efficacy Against Any Symptomatic COVID-19

Efficacy against any symptomatic COVID-19 (including mild disease) and efficacy based on a less restrictive case definition (FDA harmonized case definition), with onset at least 14 days or 28 days after vaccination, were overall similar to results obtained for the primary efficacy endpoint of efficacy against moderate to severe/critical COVID-19. There were only 4 centrally confirmed mild COVID-19 cases (1 in vaccine group, 3 in placebo group) with onset ≥14 days post-vaccination, indicating that the moderate to severe/critical primary efficacy endpoint definition captured almost all cases of symptomatic COVID-19.

Table 15. Vaccine Efficacy Against Centrally Confirmed COVID-19[a] With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
Symptomatic COVID-19, any severity[a]	117 (19514) 3116.5	351 (19544) 3095.9	66.9% (59.1, 73.4)	66 (19306) 3102.0	195 (19178) 3070.5	66.5% (55.5, 75.1)
FDA harmonized COVID-19 cases	114 (19514) 3116.6	345 (19544) 3096.3	67.2% (59.3, 73.7)	65 (19306) 3102.0	193 (19178) 3070.6	66.7% (55.6, 75.2)

Source: Sponsor tables TEFSUM01_A, TEMSUM01_C
N=Total number of participants at risk per category
[a] Includes mild, moderate, and severe/critical cases

Severe COVID-19 Cases

All COVID-19 cases which met the severe/critical definition as specified by the study protocol and all moderate cases with a total of 3 or more signs and/or symptoms were assessed independently by a clinical severity adjudication committee. Only cases classified as severe/critical by the adjudication committee are included in the severe/critical endpoint. Table 16 shows efficacy against severe/critical COVID-19 including only centrally confirmed cases and efficacy against severe/critical COVID-19 when non-centrally confirmed cases are also included.

As of the cutoff date for adjudication (January 19, 2021), there were 74 centrally confirmed, adjudicated severe/critical COVID-19 cases with an onset at least 14 days after vaccination and 39 cases with an onset at least 28 days after vaccination. Efficacy against severe disease appears to be greater when cases that occurred before 28 days are excluded. Point estimates of efficacy were lower in participants ≥60 years of age compared to participants 18 to 59 years-old when evaluating only centrally confirmed cases; however, the confidence intervals are wide. When non-centrally confirmed cases were included, the VE estimate for participants ≥60 years of age increased (and the confidence interval narrowed) and was more similar to the VE estimates for 18 to 59 year-olds and the overall population.

Table 16. Vaccine Efficacy Against Adjudicated Severe/Critical COVID-19 With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
Centrally confirmed cases[a]						
Overall	14 (19514) 3125.1	60 (19544) 3122.0	76.7% (54.6, 89.1)[b]	5 (19306) 3106.2	34 (19178) 3082.6	85.4% (54.2, 96.9)[b]
18-59 years	8 (12750) 2114.3	41 (12782) 2115.1	80.5% (57.8, 92.1)	2 (12617) 2101.0	24 (12527) 2086.7	91.7% (66.7, 99.1)
≥60	6 (6764) 1010.7	19 (6762) 1006.9	68.5% (18.1, 89.7)	3 (6689) 1005.1	10 (6651) 995.9	70.3% (-15.5, 94.7)
Including non-centrally confirmed cases						
Overall	19 (19514) 3124.7	80 (19544) 3121.0	76.3% (57.9, 87.5)	8 (19306) 3106.0	48 (19178) 3082.0	83.5% (54.2, 96.9)
18-59 years	12 (12750) 2114.0	52 (12782) 2114.5	76.9% (56.2, 88.8)	5 (12617) 2100.9	33 (12527) 2086.3	85.0% (61.2, 95.4)
≥60 years	7 (6764) 1010.7	28 (6762) 1006.4	75.1% (41.7, 90.8)	3 (6689) 1005.1	15 (6651) 995.7	80.2% (30.0, 96.3)

Source: Sponsor tables GEFBO06_A, GEFBO06_C, GEFBO05NC_A, GEFBO05NC_C
N=Total number of participants at risk per category
[a] Endpoint for severe/critical disease as specified in SAP
[b] Adjusted 95% CI

Severe cases which occurred after the cutoff date for adjudication were included in the primary

efficacy analysis but were not included as severe/critical cases, which is based on adjudicated cases only.

COVID-19 Requiring Medical Intervention

The endpoint of COVID-19 requiring medical intervention is defined as participant requiring hospitalization, ICU admission, mechanical ventilation, and/or ECMO, linked to objective measures such as decreased oxygenation, X-ray or computed tomography (CT) findings, and linked to any molecularly confirmed, COVID-19 with onset at least 14 days and at least 28 days post-vaccination. This endpoint was collected using the Medical Resource Utilization (MRU) form to be completed by the investigator on Days 3 through 5 and/or Day 29 of the COVID-19 episode. The vaccine appears to offer protection against COVID-19 requiring medical intervention starting at least 14 days post-vaccination. In the vaccine group, there were no COVID-19 cases requiring medical intervention, per MRU forms, after 28 days post-vaccination, compared to 5 such cases in the placebo group counting only centrally confirmed cases (7 cases in the placebo group counting any positive PCR).

Table 17. Vaccine Efficacy of First Occurrence COVID-19 Requiring Medical Intervention Based on MRU, With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Centrally Confirmed	2 (19514) 3126.9	8 (19544) 3126.1	75.0% (-25.3, 97.4)	0 (19306) 3106.4	5 (19178) 3084.4	
Any positive PCR	2 (19514) 3125.9	14 (19544) 3125.8	85.7% (37.8, 98.4)	0 (19306) 3106.4	7 (19178) 3084.4	100% (31.1, 100.0)

Source: Sponsor tables GEFMI03, GEFMI01, GEFMI01NCA, GEFMI01NCC
N=Total number of participants at risk per category
[a] If fewer than 6 cases are observed for an endpoint then the VE is not shown.
Abbreviation: MRU, Medical Resource Utilization

The Day 29 timepoint included in the MRU forms resulted in some cases requiring medical intervention not having MRU forms returned by the data cutoff date, and these cases were not included in the analysis above. A post hoc analysis of all COVID-19 hospitalizations was performed by counting all hospitalizations recorded in MRU forms, SAEs, and clinical event listings (e.g., during a severe/critical COVID-19 episode), in the setting of a positive PCR at the onset of the COVID-19 episode or onset of the AE. In total, 48 COVID-19 hospitalizations were identified among participants without evidence of SARS-CoV-2 PCR infection at baseline. The totality of these data indicates vaccine efficacy in the prevention of severe COVID-19 requiring hospitalization, with no COVID-19 related hospitalizations in the vaccine group following 28 days after vaccination.

Table 18. Vaccine Efficacy of First Occurrence COVID-19 Requiring Hospitalization, With Onset at Least 14 or at Least 28 Days After Vaccination, Per Protocol Set, Study 3001 (Post Hoc Analysis)

Onset After Vaccination	Ad26.COV2.S No. of Cases (Person-yrs)	Placebo No. of Cases (Person-yrs)	VE% (95% CI)
At least 1 day (FAS-seronegative at baseline)			
Centrally confirmed	6 (3202.8)	18 (3213.1)	66.6% (12.1, 89.1)
Any positive PCR	6 (3202.8)	42 (3211.6)	85.7% (66.1, 95.0)
At least 14 days			
Centrally confirmed	2 (3125.8)	11 (3125.9)	81.8% (16.7, 98.0)
Any positive PCR	2 (3125.8)	29 (3125.1)	93.1% (72.7, 99.2)
At least 28 days			
Centrally confirmed	0 (3106.3)	6 (3084.4)	100% (15.7, 100.0)
Any positive PCR	0 (3106.3)	16 (3083.9)	100% (74.3, 100.0)

Source: TEFMI04

The 2 COVID-19 related hospitalizations that occurred at least 14 days after vaccination in the vaccine group were both participants ≥60 years of age with comorbidities (obesity and hypertension). In the subgroup of participants ≥60 years with comorbidities, 2 of 22 total moderate to severe/critical COVID-19 cases in vaccine recipients resulted in hospitalization (both prior to 28 days) compared to 11 of 63 moderate to severe/critical cases in placebo recipients (with 5 occurring after 28 days).

COVID-19 Related Deaths

As of February 5, 2021, there were 7 COVID-19-related deaths reported in the study. All participants had a documented positive SARS-CoV-2 RT-PCR around the time of the event, but not all have been centrally confirmed to date. All 7 deaths occurred in the placebo group and were in study sites in South Africa. All of these participants had one or more comorbidities which placed them at higher risk for severe COVID-19. One death was in a participant PCR positive at baseline, who had onset of illness 10 days after vaccination. These results suggest that the vaccine is efficacious against mortality associated with COVID-19. Outcomes related to an exploratory all-cause mortality endpoint are discussed in a separate section below.

Table 19. COVID-19 Related Deaths

Arm	Study Day[c]	Age	Comorbidity
Placebo	15	63	Obesity, Hypertension
Placebo	18[a]	52	Obesity, Diabetes
Placebo	31	54	Obesity, Hypertension, Diabetes, Heart failure
Placebo	38	49	Obesity, Hypertension
Placebo	39	68	Obesity
Placebo	49[b]	60	Obesity
Placebo	55	60	Asthma

[a] Participant with positive SARS-CoV-2 PCR at baseline
[b] Reported after the primary analysis cutoff date of January 22, 2021
[c] Study day of death

Vaccine Efficacy Against Asymptomatic Infections

The secondary endpoint for asymptomatic infection was defined in the protocol as a participant who does not fulfill the criteria for suspected COVID-19 based on signs and symptoms (further specified as no symptoms on the day preceding, the day of, or any time after the positive PCR test) AND has a SARS-CoV-2 positive RT-PCR test result OR develops a positive serology

based on a SARS-CoV-2 N-specific immunoglobulin assay (Elecsys®, Roche) during the study. SARS CoV-2 seropositivity by non-S protein was assessed at Day 1 (pre-vaccination), Day 29 (28 days post-vaccination), and Day 71. On manual review of the cases included in this endpoint, the Sponsor identified multiple cases in which the participants were symptomatic 2 days or more prior to the positive PCR or serology test. Manual review identified 2 centrally-confirmed cases in the vaccine group which were classified as asymptomatic based on the statistical analysis plan (SAP) but would meet the moderate case definition, and one centrally-confirmed SAP-classified asymptomatic case in the placebo group which would meet the mild case definition, with onset after 14 days post-vaccination. These cases were not included in the primary or secondary efficacy analyses, which are based on SAP-defined cases, but are not expected to significantly change the efficacy results. To remove possibly symptomatic COVID-19 cases from the analysis of asymptomatic infection, the Sponsor conducted a post hoc analysis including only participants without COVID-19 symptoms since screening.

As specified in the SAP, the secondary endpoint of efficacy against all SARS-CoV-2 infection with onset from Day 29 (including asymptomatic infection) will only be tested when at least 15,000 participants with Day 71 serology are available, and the secondary endpoint of efficacy against asymptomatic or undetected infection with onset from Day 29 will only be tested when all participants have at least 6 months of follow-up.

From Day 1 through Day 29, the data show only modest, non-statistically significant vaccine efficacy against asymptomatic SARS-CoV-2 infection. Analysis of the Day 29 and after timepoint shown below is based on an interim analysis of Day 71 serology results from 2,892 participants. These individuals represent 28.8% of the 10,045 participants who had completed the Day 71 visit by the data cutoff date of January 22 (serology results cutoff February 8). The percentage of available serology results are not evenly distributed across study sites (range: 16.9% of study participants in Chile to 68.4% of participants in South Africa). Although these results may suggest potential efficacy against asymptomatic infection after Day 29, this observation should be interpreted with caution as follow-up time is limited, and only a small percentage of participants had available N-serology data to contribute to this endpoint. This analysis was also done at an interim time point not pre-specified by the SAP.

Table 20. Vaccine Efficacy Against Asymptomatic SARS-CoV-2 Infections, Full Analysis Set

	Day 1-Day 29			After Day 29[e]		
	Ad26.COV2.S No. of Cases (Person-yrs)	**Placebo No. of Cases (Person-yrs)**	**VE% (95% CI)**	**Ad26.COV2.S No. of Cases (Person-yrs)**	**Placebo No. of Cases (Person-yrs)**	**VE% (95% CI)**
FAS seronegative at baseline	N=19739	N=19809		N=19301	N=19162	
+PCR and/or serology[b]	159 (1561.3)	182 (1564.1)	12.5% (-8.9, 29.7)	22 (3099.7)	54 (3064.2)	59.7% (32.8; 76.6)
+PCR and/or serology without previous symptoms[b,d]	87 (1556.2)	109 (1559.3)	20.0% (-7.0, 40.4)	10 (3098.0)	38 (3061.5)	74.0% (46.8; 88.4)
Serology risk set[a]	N=14084	N=14019		N=1346	N=1304	
Seroconverted[c]	153 (1114.3)	175 (1108.2)	13.1% (-8.6, 30.5)	18 (312.2)	50 (298.8)	65.5% (39.9; 81.1)

	Day 1-Day 29			After Day 29[e]		
	Ad26.COV2.S No. of Cases (Person-yrs)	Placebo No. of Cases (Person-yrs)	VE% (95% CI)	Ad26.COV2.S No. of Cases (Person-yrs)	Placebo No. of Cases (Person-yrs)	VE% (95% CI)
Seroconverted without previous symptoms[c,d]	84 (1109.4)	108 (1103.7)	22.6% (-3.9, 42.5)	10 (310.9)	37 (296.6)	74.2% (47.1; 88.6)

[a] Serology risk set: Participants with a non-S protein serology result available on Day 29 or Day 71
[b] A participant will be considered to have experienced asymptomatic or undetected COVID-19 if the participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms as detected by the algorithm described in the SAP; 1) no symptoms on the day before, at or after the PCR positive test and 2) has a SARS-CoV-2 positive RT-PCR/molecular test result or develops a positive serology (non-S protein) test
[c] A participant will be considered serologically converted if the participant develops a positive serology (non-S protein) test without a SARS-CoV-2 positive RT-PCR before the positive serology test irrespective of whether previous symptoms occurred
d A participant is considered without previous symptoms if no COVID-19 symptoms occurred before the positive PCR or serology test at any point in time during the study
[e] N (for at risk set and serology risk set) for >Day 29 analysis based on Per Protocol Set
Source: Sponsor tables TEFSUM02B, TEFSUM02C, CSR addendum submitted February 12, 2021

Exploratory Efficacy Analyses

Additional vaccine efficacy analyses were conducted and described below.

Effect on All-Cause Mortality

As of the cutoff date for the primary analysis, 19 deaths were reported in the study. Of these 19 deaths, 6 were related to COVID-19, all in the placebo group. There is suggestion of a positive effect on all-cause mortality; however, the confidence interval is wide, with a lower bound below 0 after 28 days post-vaccination.

Table 21. Effect on All-Cause Mortality, Full Analysis Set

	Ad26.COV2.S N=21895 No. of Cases (Person-yrs)	Placebo N=21888 No. of Cases (Person-yrs)	VE% (95% CI)
At least 1 day after vaccination[a]	3 (3544.8)	16 (3542.2)	81.3% (34.6, 96.5)
At least 14 days after vaccination	3 (3544.8)	15 (3541.9)	80.0% (29.4, 96.3)
At least 28 days after vaccination	2 (3544.3)	8 (3540.7)	75% (-25.2, 97.4)

[a] Cases in the later timepoints are included in the earlier timepoint
Source: GEFACM01B1, GEFACM01B28, GEFACM01B14

An update on deaths reported from the time period of January 22 to February 5 included an additional 6 deaths. Of these 6 deaths, 2 occurred in the vaccine group and 4 occurred in the placebo group. One of the cases in the placebo group and none in the vaccine group was related to COVID-19.

Sequencing Data from Centrally Confirmed COVID-19 Cases

During the conduct of Study 3001 (September 21, 2020 through the data cutoff date of January 22, 2021), new SARS-CoV-2 variants emerged in geographical regions where the study took place. In a subgroup analysis of vaccine efficacy against moderate to severe/critical COVID-19 in the United States, South Africa, and Brazil, there was lower efficacy observed in South Africa compared to the United States. Vaccine efficacy against severe/critical COVID-19 was comparably high across the three countries, although there was a wide confidence interval around the point estimates for the United States and Brazil.

Table 22. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical and Severe/Critical COVID-19 Including Non-centrally Confirmed Cases With Onset at Least 14 or at Least 28 Days After Vaccination, by Country of Participation, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Country Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] 95% CI	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
United States						
Moderate to severe/critical	51 (9119) 1414.0	196 (9086) 1391.3	74.4% (65.0, 81.6)	32 (8958) 1403.4	112 (8835) 1375.6	72.0% (58.2, 81.7)
Severe/critical	4 (9119) 1417.2	18 (9086) 1404.8	78.0% (33.1, 94.6)	1 (8958) 1405.2	7 (8835) 1382.2	85.9% (-9.4, 99.7)
South Africa						
Moderate to severe/critical	43 (2473) 377.6	90 (2496) 379.2	52.0% (30.3, 67.4)	23 (2449) 376.1	64 (2463) 376.9	64.0% (41.2, 78.7)
Severe/critical	8 (2473) 380.2	30 (2496) 382.9	73.1% (40.0, 89.4)	4 (2449) 377.0	22 (2463) 379.0	81.7% (46.2, 95.4)
Brazil						
Moderate to severe/critical	39 (3370) 555.7	114 (3355) 548.8	66.2% (51.0, 77.1)	24 (3354) 554.8	74 (3312) 546.1	68.1% (48.8, 80.7)
Severe/critical	2 (3370) 558.9	11 (3355) 556.8	81.9% (17.0, 98.1)	1 (3354) 556.2	8 (3312) 549.8	87.6% (7.8, 99.7)

Source: Sponsor tables GEFPE09A, GEFPE09C, GEFBO05NC_A, GEFBO05NC_C
N=Total number of participants at risk per category

Strain sequencing of COVID-19 cases in Study 3001 to inform the vaccine efficacy analysis by region is ongoing. As of February 12, 2021, 71.7% of centrally confirmed primary analysis cases have been sequenced. In the United States, 73.5% of cases have been sequenced, of which 96.4% were identified as the SARS-CoV-2 Wuhan-H1 variant D614G. In South Africa, 66.9% of cases have been sequenced, of which 94.5% were identified as 20H/501Y.V2 variant (B.1.351). In Brazil, 69.3% of cases have been sequenced, of which 69.4% were identified as variant of the P.2 lineage and 30.6% were identified as the Wuhan-H1 variant D614G. As of February 12, 2021, there were no sequenced cases from the B1.1.7 or P.1 lineages. Because strain sequencing of all COVID-19 cases in the study is incomplete at the time of this analysis, and due to selection bias involved in prioritizing the cases to be sequenced first (moderate to severe/critical cases, cases with onset at least 14 days after vaccination, samples with viral load >200 copies/mL), vaccine efficacy against specific SARS-CoV-2 variants cannot be evaluated at this time.

Efficacy Summary

The data from the primary efficacy analysis, with a cutoff date of January 22, 2021, and median follow-up for efficacy of 2 months post-vaccination, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent protocol-defined moderate to severe/critical COVID-19 occurring at least 14 days after vaccination was 66.9% (95% CI 59.0; 73.4), and 66.1% (95% CI 55.0; 74.8) for moderate to severe/critical COVID-19 occurring at least 28 days after vaccination, in participants without prior evidence of SARS-CoV-2 infection. Results for the secondary endpoint of vaccine efficacy against protocol-defined

symptomatic COVID-19 of any severity (mild, moderate, or severe/critical) were similar to those of the primary endpoint of vaccine efficacy against moderate to severe/critical disease. For prevention of centrally confirmed, adjudicated severe/critical disease, vaccine efficacy (95% CI) was 76.7% (54.6, 89.1) with onset at least 14 days after vaccination and 85.4% (54.2, 96.9) with onset at least 28 days after vaccination. In a post hoc analysis of all COVID-19 related hospitalizations starting 14 days after vaccination, including non-centrally confirmed cases, there were 2 cases in the vaccine group (with no cases after 28 days) compared with 29 cases in the placebo group (with 16 cases after 28 days). The evaluation of vaccine efficacy against asymptomatic disease and its interpretation are limited at this time, since the measurements were performed in a small subset of participants.

Efficacy estimates across demographic subgroups in supportive analyses of primary and secondary endpoints were generally consistent with the efficacy estimates in the overall study population, but the small numbers of participants and cases in certain subgroups (e.g., certain racial subgroups, individual comorbid conditions) limit the interpretability of subgroup-specific efficacy results. Neither age nor presence of comorbidities alone impacted the efficacy estimates for the primary endpoints of moderate to severe/critical COVID-19, with the exception of a lower efficacy estimate for COVID-19 with onset at least 28 days post-vaccination in participants with comorbidities compared to those without comorbidities (Table 10 and Table 13).

The efficacy estimate for moderate to severe/critical COVID-19 with onset at least 28 days post-vaccination was lower for the subgroup of participants ≥60 years of age with comorbidities than for younger participants and participants ≥60 years of age without comorbidities (Table 13). Confidence intervals for efficacy estimates across subgroups generally overlapped, and efficacy estimates in participants ≥60 years of age with comorbidities increased as the number of cases included in the analysis increased (i.e., with inclusion of non-centrally confirmed cases and cases starting at 14 days post-vaccination), indicating that lower efficacy estimates in this subgroup potentially reflect imprecision associated with smaller numbers of cases. Efficacy estimates against centrally confirmed severe/critical COVID-19 were reduced in participants ≥60 years of age as compared to younger participants, but there was no meaningful reduction when cases not yet centrally confirmed were included in the analysis (Table 16). The two hospitalizations in vaccine recipients due to COVID-19 with onset at least 14 days post-vaccination occurred in participants ≥60 years of age with comorbidities (as compared to 11 hospitalizations in placebo recipients ≥60 years of age with comorbidities). No vaccine recipients were hospitalized due to COVID-19 with onset at least 28 days post-vaccination.

To explore the possible impact of circulation of variant strains on vaccine efficacy, a subgroup analysis of vaccine efficacy against moderate to severe/critical and severe/critical COVID-19 was done for the United States, South Africa, and Brazil. There was a lower efficacy against moderate to severe/critical disease endpoints observed in South Africa [52.0% (95% CI 30.3, 67.4) and 64.0% (95% CI 41.2, 78.7) starting 14 days and 28 days after vaccination, respectively] compared to the United States (74.4% (65.0, 81.6) and 72.0% (58.2, 81.7) starting 14 days and 28 days after vaccination, respectively), but vaccine efficacy against severe/critical COVID-19 at the two timepoints were similarly high in all 3 countries. Strain sequencing of COVID-19 cases in the study to inform the vaccine efficacy analysis by region is ongoing. As of February 12, 2021, 71.7% of central laboratory confirmed primary analysis cases have been sequenced. In the U.S., 96.4% of the sequenced cases were identified as the SARS-CoV-2 Wuhan-H1 variant D614G. In South Africa, 94.5% of the sequenced cases were identified as 20H/501Y.V2 variant (B.1.351). In Brazil, 69.4% were identified as variant of the P.2 lineage and

30.6% were identified as the Wuhan-H1 variant D614G. As of February 12, 2021, there were no cases identified from B.1.1.7 or P1 lineages.

5.2.6 Safety

The safety analyses presented in this review are derived from safety data available through the cutoff date of January 22, 2021.

The protocol specified safety monitoring for the following:

- Solicited local and systemic reactions during the 7 days following vaccination in the safety subset (N=6,736)
- Unsolicited AEs during the 28 days following vaccination in the safety subset
- MAAEs during the 6 months following vaccination in the FAS (N=43,783)
- SAEs and AEs leading to study discontinuation for the duration of the study in the FAS

Overall, the proportions of participants with MAAEs, SAEs, and deaths were balanced between the vaccine and placebo groups. Rates of unsolicited AEs were also balanced across treatment groups; however, a greater percentage of participants in the vaccine group had unsolicited AEs considered to be related to the study product. As compared to the placebo group, a greater percentage of participants in the vaccine group experienced local and systemic solicited ARs. Rates of ARs were lower in participants ≥60 years of age compared to participants 18 to 59 years of age. The table below summarizes rates of AEs by treatment group and age group.

Table 23. Participants Reporting at Least One Adverse Event, Among All Participants and by Age Group

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Full analysis set	**N=21895**	**N=21888**
Medically attended adverse event	304/21895 (1.4)	408/21888 (1.9)
18-59 years of age	207/14564 (1.4)	272/14547 (1.9)
≥60 years of age	97/7331 (1.3)	136/7341 (1.9)
Related[b] medically attended adverse events	22/21895 (0.1)	22/21888 (0.1)
18-59 years of age	15/14564 (0.1)	18/14547 (0.1)
≥60 years of age	7/7331 (0.1)	4/7341 (0.1)
Serious adverse event	83/21895 (0.4)	96/21888 (0.4)
18-59 years of age	45/14564 (0.3)	56/14547 (0.4)
≥60 years of age	38/7331 (0.5)	40/7341 (0.5)
Related[b] serious adverse event	7/21895 (<0.1)	2/21888 (<0.1)[c]
18-59 years of age	4/14564 (<0.1)	1/14547 (<0.1)
≥60 years of age	3/7331 (<0.1)	1/7341 (<0.1)
Deaths	3/21895 (<0.1)	16/21888 (0.1)
18-59 years	1/14564 (<0.1)	7/14547 (<0.1)
≥60 years	2/7331 (<0.1)	9/7341 (0.1)
Related[b] deaths	0	0
AE leading to study discontinuation	0	0
Safety subset	**N=3356**	**N=3380**
Solicited local adverse reaction	1685/3356 (50.2)	657 /3380 (19.4)
18-59 years of age	1218/2036 (59.8)	413/2049 (20.2)
≥60 years of age	467/1320 (35.4)	244/1331 (18.3)
Grade 3 solicited local adverse reaction[a]	23/3356 (0.7)	6/3380 (0.2)
18-59 years of age	18/2036 (0.9)	4/2049 (0.2)
≥60 years of age	5/1320 (0.4)	2/1331 (0.2)

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Solicited systemic adverse reaction	1850/3356 (55.1)	1185/3380 (35.1)
18-59 years of age	1252/2036 (61.5)	745/2049 (36.4)
≥60 years of age	598/1320 (45.3)	440/1331 (33.1)
Grade 3 solicited systemic adverse reaction[a]	61/3356 (1.8)	21/3380 (0.6)
18-59 years of age	47/2036 (2.3)	12/2049 (0.6)
≥60 years of age	14/1320 (1.1)	9/1331 (0.7)
Unsolicited adverse event up to 28 days after vaccination	440/3356 (13.1)	407/3380 (12.0)
18-59 years of age	285/2036 (14.0)	275/2049 (13.4)
≥60 years of age	155/1320 (11.7)	132/1331 (9.9)
Grade 3 unsolicited adverse event	16/3356 (0.5)	16/3380 (0.5)
18-59 years of age	10/2036 (0.5)	10/2049 (0.5)
≥60 years of age	6/1320 (0.5)	6/1331 (0.5)
Grade 4 unsolicited adverse event	3/3356 (0.1)	2/3380 (0.1)
18-59 years of age	2/2036 (0.1)	2/2049 (0.1)
≥60 years of age	1/1320 (0.1)	0/1331 (0.0)
Related[b] unsolicited adverse events	242/3356 (7.2)	154/3380 (4.6)
18-59 years of age	163/2036 (8.0)	96/2049 (4.7)
≥60 years of age	79/1320 (6.0)	58 /1331 (4.4)

Source: Sponsor tables TSFAE04, TSFAE05, TSFAESOLLOC27, TSFAESOLSYS27, TSFAESOL02, TSFAEUNSOL01 & TSFAEUNSOL12.
n = number of participants with specified event; N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
[a]There were no reports of Grade 4 solicited adverse reactions
[b] Related as assessed by investigator
[c] 1 participant reported 2 SAEs

The following issues were identified during the safety review:

1. Several reports of solicited reactions and non-serious, unsolicited adverse events were omitted from the analyses due to incorrectly coded start dates. However, the omissions did not have a major impact on the estimated event rates (0% to 0.3% of the safety subset of the respective treatment group) and thus did not impact the safety conclusions.

2. Discrepancies were identified between the number of solicited reactions reported by participants in source documents and the number of events reported by the investigator and included in the datasets upon which the safety analyses were based. In response to an FDA information request, the Sponsor conducted queries of potential missing clinical event data for 210 subjects, of which 40% of the queried events were determined to not meet reporting criteria (e.g., participants who did not experience any solicited symptom during the planned 7-day evaluation period or those who experienced an event with toxicity <grade 1). Other than 44 open queries, the remaining queries resulted in corrected reporting of previously missing clinical event data to the relevant datasets that will be included in final safety analyses with the submission of the licensure application. However, based on FDA evaluation of the impacted data, and the fact that these participants represent a small proportion of the safety subset, the corrected solicited ARs are expected to have a minor impact on the rates submitted by the Sponsor in its EUA request.

Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination were assessed across groups and are presented in the tables below stratified by age (18 to 59 years; ≥60 years) for participants in the safety subset (N=6,736). Solicited ARs were recorded daily by

study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema and swelling) and systemic reactions (fatigue, headache, myalgia, nausea and fever).

Local Adverse Reactions

Solicited local ARs were reported at higher rates in vaccine recipients than placebo recipients. The proportions of participants reporting any local AR were 50.2% and 19.4% in vaccine and placebo groups, respectively. The proportions reporting at least one grade 3 local AR were 0.7% and 0.2% in vaccine and placebo groups, respectively. There were no reports of grade 4 local reactions in either group.

The most frequently reported local AR was injection site pain, reported by 48.6% of vaccine recipients and 16.7% of placebo recipients. Grade 3 pain was reported in 0.3% of vaccine recipients and <0.1% of placebo recipients. Erythema (vaccine versus placebo: 7.3% versus 3.9%) and swelling (5.3% versus 1.6%) were reported less frequently.

All local ARs were reported more frequently among younger (18-59 years) than older (≥60 years) participants. Among participants in the vaccine group, injection site pain was reported in 58.6% of 18-59-year-olds and 33.3% of ≥60-year-olds. Erythema and swelling were similarly reported at higher rates among younger than older participants in the vaccine group (Table 24).

Among participants in the vaccine group, the overall rate of local ARs was similar between those who were seronegative for SARS-CoV-2 at baseline (n=3,202) and those who were seropositive at baseline (n=154): 50.0% versus 53.9%. Rates for local ARs by baseline serostatus were as follows (seronegative vs. seropositive): injection site pain 48.4% vs. 53.2%; swelling 5.2% vs. 6.5%; erythema 7.4% vs. 4.5%.

The table below provides rates of local ARs by treatment group and age group.

Table 24. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Vaccination, Safety Subset[a], Study 3001

Adverse Reaction	18-59 Years Ad26.COV2.S N=2036 n (%)	18-59 years Placebo N=2049 n (%)	≥60 Years Ad26.COV2.S N=1320 n (%)	≥60 Years Placebo N=1331 n (%)
Any Local	1218 (59.8%)	413 (20.2%)	467 (35.4%)	244 (18.3%)
Grade 3	18 (0.9%)	4 (0.2%)	5 (0.4%)	2 (0.2%)
Pain[b]	1193 (58.6%)	357 (17.4%)	439 (33.3%)	207 (15.6%)
Grade 3	8 (0.4%)	0	3 (0.2%)	2 (0.2%)
Erythema[c]	184 (9.0%)	89 (4.3%)	61 (4.6%)	42 (3.2%)
Grade 3	6 (0.3%)	2 (0.1%)	1 (0.1%)	0
Swelling[b]	142 (7.0%)	32 (1.6%)	36 (2.7%)	21 (1.6%)
Grade 3	5 (0.2%)	2 (0.1%)	2 (0.2%)	0

Source: Sponsor Table TSFAESOLLOC27
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
[b] Pain- Grade 3: any use of Rx pain reliever/prevents daily activity;
[c] Erythema and Swelling/Induration- Grade 3: >100mm;
Note: No grade 4 solicited local adverse reactions were reported.

The median time to onset of local ARs was within 2 days of vaccination, and the median duration was 2 days for erythema and pain and 3 days for swelling. Pain was reported to last greater than 7 days in 2.3% of participants in the vaccine group and 2.1% of participants in the

placebo group. Among participants in the vaccine group, erythema and swelling had a duration >7 days in 0.8% and 0.5% of participants, respectively.

The table below provides time to onset and duration of local ARs by treatment group.

Table 25. Time (Days) to Onset and Duration of Solicited Local Adverse Events, Safety Subset[a], Study 3001

Adverse Reaction	Ad26.COV2.S N=3356	Placebo N=3380
Pain, n (%)	1632 (48.6%)	564 (16.7%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 67)	2.0 (1, 67)
>7 days duration	38 (2.3%)	14 (2.1%)
Erythema, n (%)	245 (7.3%)	131 (3.9%)
Median time to onset (min, max)	2.0 (1, 7)	1.0 (1, 8)
Median duration (min, max)	2.0 (1, 9)	2.0 (1, 19)
>7 days duration	13 (0.8%)	4 (0.6%)
Swelling, n (%)	178 (5.3%)	53 (1.6%)
Median time to onset (min, max)	2.0 (1, 8)	1.0 (1, 8)
Median duration (min, max)	3.0 (1, 14)	1.0 (1, 19)
>7 days duration	9 (0.5%)	2 (0.3%)

Source: Sponsor Table TSFAESOLLOC25
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

Systemic Adverse Reactions

Solicited systemic ARs were reported at higher rates in vaccine than placebo recipients. The proportions of participants reporting any systemic ARs were 55.1% in the vaccine group and 35.1% in the placebo group. The proportions reporting at least one grade 3 systemic AR were 1.8% in the vaccine group and 0.6% in the placebo group. There were no reports of grade 4 systemic reactions in either group.

The most frequently reported systemic ARs were headache (vaccine versus placebo: 38.9% versus 23.7%) and fatigue (38.2% versus 21.5%). Rates of other systemic ARs in the vaccine versus placebo groups were as follows: myalgia (33.2% versus 12.7%); nausea (14.2% versus 9.7%); and fever (9.0% versus 0.6%).

Grade 3 systemic ARs were reported infrequently. The most frequently reported grade 3 systemic ARs were fatigue and myalgia, reported in 1.0% vs 0.3% and 1.0% vs. 0.2% of vaccine recipients and placebo recipients, respectively. Grade 3 fever (102.1-104°F) was reported in 0.2% of vaccine recipients and no placebo recipients.

Among participants in the vaccine group, all systemic ARs were reported more frequently among younger (18-59 years) than older (≥60 years) participants, although nausea was reported at more similar rates: 15.5% in participants 18-59 years and 12.3% in participants ≥60 years. Among vaccine group participants, rates of other systemic ARs by age group were as follows (18-59 and ≥60 years): headache (44.4% and 30.4); fatigue (43.8% and 29.7%); myalgia (39.1% and 24.0%); fever (12.8% and 3.1%).

A higher percentage of participants in the vaccine group used antipyretics/analgesics in the 7 days following vaccination compared to participants the placebo group; 19.9% versus 5.7%. This was primarily driven by participants 18-59 years old. Among participants in the vaccine group, 26.4% of those 18-59 years used antipyretics/analgesics compared to 9.8% of those ≥60 years old.

The overall rate of systemic ARs was similar in vaccine recipients who were seronegative for SARS-CoV-2 at baseline (n=3,202) and those who were seropositive at baseline (n=154): 55.4% versus 50.0%. Rates for systemic ARs by baseline serostatus were as follows (seronegative vs. seropositive): headache 38.9% vs. 38.3%; fatigue 38.3% vs. 37.0%; myalgia 33.2% vs. 32.5%; nausea 14.3% vs. 12.3%; fever 9.1% vs. 6.5%.

The table below provides rates of systemic ARs by treatment group and age group.

Table 26. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Vaccination, Safety Subset[a], Study 3001

Adverse Reaction	Ad26.COV2.S 18-59 Years N=2036 n/N (%)	Placebo 18-59 Years N=2049 n/N (%)	Ad26.COV2.S ≥60 Years N=1320 n/N (%)	Placebo ≥60 Years N=1331 n/N (%)
Any Systemic	1252 (61.5%)	745 (36.4%)	598 (45.3%)	440 (33.1%)
Grade 3	47 (2.3%)	12 (0.6%)	14 (1.1%)	9 (0.7%)
Fatigue[b]	891 (43.8%)	451 (22.0%)	392 (29.7%)	277 (20.8%)
Grade 3	25 (1.2%)	4 (0.2%)	10 (0.8%)	5 (0.4%)
Headache[b]	905 (44.4%)	508 (24.8%)	401 (30.4%)	294 (22.1%)
Grade 3	18 (0.9%)	5 (0.2%)	5 (0.4%)	4 (0.3%)
Myalgia[b]	796 (39.1%)	248 (12.1%)	317 (24.0%)	182 (13.7%)
Grade 3	29 (1.4%)	1 (<0.1%)	3 (0.2%)	5 (0.4%)
Nausea[c]	315 (15.5%)	183 (8.9%)	162 (12.3%)	144 (10.8%)
Grade 3	3 (0.1%)	3 (0.1%)	3 (0.2%)	3 (0.2%)
Fever[d]	261 (12.8%)	14 (0.7%)	41 (3.1%)	6 (0.5%)
Grade 3	7 (0.3%)	0	1 (0.1%)	0
Antipyretic/Analgesic Use	538 (26.4%)	123 (6.0%)	130 (9.8%)	68 (5.1%)

Source: Sponsor table TSFAESOLSYS27
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
[b] Fatigue, Headache, Myalgia – Grade 3: incapacitating; prevents daily activity; use of Rx pain reliever. Grade 4: Requires E.R. visit or hospitalization
[c] Nausea –Grade 3: incapacitating; prevents daily activity. Grade 4: Requires E.R. visit or hospitalization
[d] Fever - Grade 3: ≥39.0 to ≤40.0°C or ≥102.1 to ≤104.0° F; Grade 4: >40.0°C or >104.0°F
Note: No grade 4 solicited local adverse reactions were reported.

Among participants in the vaccine group, the median time to onset of all solicited systemic ARs was within 2 days of vaccination. Median durations of systemic reactions in vaccine group participants were as follows: 2 days for fatigue, headache, and myalgia and 1 day for nausea and fever. Systemic reactions with a duration longer than 7 days were reported in vaccinated participants for all systemic ARs with the exception of fever. Percentages of vaccine group participants reporting systemic ARs with duration longer than 7 days were as follows: fatigue 1.6%, myalgia 1.1%, headache 0.7%, nausea 0.3%.

The table below provides time to onset and duration of systemic ARs by treatment group.

Table 27. Time (Days) to Onset and Duration of Solicited Adverse Events, Safety Subset[a], Study 3001

Adverse Reaction	Ad26.COV2.S N=3356	Placebo N=3380
Fatigue, n (%)	1283 (38.2%)	728 (21.5%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 113)	2.0 (1, 110)
>7 days duration	29 (1.6%)	25 (2.1%)
Headache, n (%)	1306 (38.9%)	802 (23.7%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 68)	1.0 (1, 62)
>7 days duration	13 (0.7%)	8 (0.7%)
Myalgia, n (%)	1113 (33.2%)	430 (12.7%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 32)	2.0 (1, 44)
>7 days duration	20 (1.1%)	15 (1.3%)
Nausea, n (%)	477 (14.2%)	327 (9.7%)
Median time to onset (min, max)	2.0 (1, 8)	3.0 (1, 8)
Median duration (min, max)	1.0 (1, 15)	1.0 (1, 8)
>7 days duration	5 (0.3%)	4 (0.3%)
Fever, n (%)	302 (9.0%)	20 (0.6%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 5)
Median duration (min, max)	1.0 (1, 7)	1.0 (1, 3)
>7 days duration	0	0

Source: Sponsor Table TSFAESOLSYS25
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

Unsolicited AEs

Through the January 22, 2021 data cutoff, 54.6% of participants in the FAS (N=43,783) had at least 2 months of follow-up. The median duration of follow-up post-vaccination for all participants was 58 days. In the safety subset (N=6,736), 99.9% of participants completed the study through Day 28. The following unsolicited AEs were specified in the protocol:

- Unsolicited AEs during the 28 days following vaccination in the safety subset
- MAAEs during the 6 months following vaccination in the FAS
- SAEs for the duration of the study in the FAS
- AEs leading to discontinuation from study participation in the FAS

Additional unsolicited AEs collected from the spontaneous reports were also analyzed in the FAS. Determination of severity for all unsolicited AE were made by investigator assessment based on definitions of severity as grades 1 through 4 (mild to potentially life threatening). Causal relationship to study vaccine was determined by study investigator and classified as "related" or "not related."

AEs associated with molecularly confirmed SARS-CoV-2 infection were not included in the analysis of AEs.

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs in the safety subset that occurred within 28 days of vaccination and at rates of ≥1% in the vaccine group. The proportions of participants with

unsolicited AE were 13.1% and 12.0% in the vaccine and placebo groups, respectively. Overall, rates of unsolicited adverse events, including events grade 3 or higher, were similar between the treatment groups.

Table 28. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Safety Subset[a], Study 3001

System Organ Class Preferred Term	Ad26.COV2.S N=3356 Any Grade n (%)	Ad26.COV2.S N=3356 ≥Grade 3 n (%)	Placebo N=3380 Any Grade n (%)	Placebo N=3380 ≥Grade 3 n (%)
General disorders and administration site	211 (6.3%)	5 (0.1%)	134 (4.0%)	2 (0.1%)
Chills	67 (2.0%)	1 (<0.1%)	19 (0.6%)	0
Fatigue	64 (1.9%)	1 (<0.1%)	77 (2.3%)	1 (<0.1%)
Vaccination site pain	42 (1.3%)	1 (<0.1%)	22 (0.7%)	0
Musculoskeletal and connective tissue disorders	103 (3.1%)	3 (0.1%)	89 (2.6%)	4 (0.1%)
Myalgia	49 (1.5%)	0	58 (1.7%)	2 (0.1%)
Arthralgia	35 (1.0%)	1 (<0.1%)	24 (0.7%)	2 (0.1%)
Nervous system disorders	98 (2.9%)	3 (0.1%)	108 (3.2%)	5 (0.1%)
Headache	72 (2.1%)	1 (<0.1%)	82 (2.4%)	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	93 (2.8%)	3 (0.1%)	88 (2.6%)	4 (0.1%)
Nasal congestion	40 (1.2%)	1 (<0.1%)	38 (1.1%)	2 (0.1%)
Cough	33 (1.0%)	1 (<0.1%)	33 (1.0%)	0
Gastrointestinal disorders	87 (2.6%)	2 (0.1%)	90 (2.7%)	2 (0.1%)
Diarrhea	33 (1.0%)	2 (0.1%)	35 (1.0%)	0
Infections and infestations	57 (1.7%)	3 (0.1%)	87 (2.6%)	6 (0.2%)

Source: Sponsor Tables TSFAEUNSOL02_D & TSFAEUNSOL03_D
[a] safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.2% of vaccine recipients and 4.6% of placebo recipients. The proportions of participants who reported grade 3 or higher unsolicited AEs were 0.6% following vaccine (19 participants) and 0.5% following placebo (18 participants).

Unsolicited Adverse Events of Clinical Interest

FDA conducted both broad and narrow Standardized MedDRA Queries (SMQs) using FDA-developed software to evaluate unsolicited adverse events of clinical interest by searching preferred terms (PTs) that could together represent various conditions, including but not limited to allergic, neurologic, inflammatory, vascular, and autoimmune disorders. Narrow searches were done to identify cases highly likely to be the condition of interest whereas broad searches were done to identify all possible cases. Ten SMQs (broad and narrow combined) were conducted on AEs reported through the data cutoff date (requiring 2 months median follow-up following vaccination) and included events that occurred in the FAS (N=43,783). AEs in the FAS were collected through protocol specified collection methods as well as spontaneous reporting by study participants.

SMQs and associated PTs for which adverse events were reported at higher rates in vaccine recipients compared to placebo recipients are discussed below. For the additional SMQs, rates were comparable between vaccine and placebo recipients.

The SMQ for "embolic and thrombotic events" in the FAS demonstrated a slight numerical imbalance; data through the cutoff date includes reports of such events among 0.06% of vaccine recipients (15 events in 14 participants) compared to 0.05% of placebo recipients (10 events in 10 participants). By PT, deep vein thrombosis (including PTs for "deep vein thrombosis," "venous thrombosis limb" and "embolism venous") was reported in 6 vaccine recipients (5 events within 28 days of vaccination) and 2 placebo recipients (2 events within 28 days of vaccination). Pulmonary embolism was reported in 4 vaccine recipients (2 events within 28 days of vaccination) and 1 placebo recipient (1 event within 28 days of vaccination). Cerebrovascular events (including PTs "cerebral infarction", "transverse sinus thrombosis", "hemiparesis", "cerebrovascular accident", "carotid artery occlusion" and "ischemic stroke") were reported in 3 vaccine recipients (4 events, 3 events within 28 days of vaccination) and 3 placebo recipients (3 events within 28 days of vaccination). Myocardial infarction was reported in 1 vaccine recipient (1 event within 28 days of vaccination) and 3 placebo recipients (2 events within 28 days of vaccination). One placebo recipient reported thrombosed hemorrhoids within 28 days of vaccination. Table 29 summarizes thromboembolic events in both vaccine and placebo recipients including investigator assessment of grade, seriousness and causality.

Table 29. Thromboembolic Events in Vaccine and Placebo Recipients, Full Analysis Set, Study 3001

Investigational Product	Adverse Event (PT)	Age/Sex	Day of Onset	Resolution Status	Grade/SAE[a]	Related[a]
Ad26.COV2.S	Deep vein thrombosis	90/M	13	Resolving	2/N	No
Ad26.COV2.S	Deep vein thrombosis	42/M	19	Unresolved	2/N	No
Ad26.COV2.S	Deep vein thrombosis	63/M	22	Resolved	4/Y	No
Ad26.COV2.S	Venous thrombosis limb	63/M	23	Resolved	2/N	No
Ad26.COV2.S	Deep vein thrombosis	52/M	27	Resolving	2/N	Yes
Ad26.COV2.S	Embolism venous	72/M	36	Unresolved	2/Y	No
Ad26.COV2.S	Pulmonary embolism	30/F	3	Resolved	4/Y	No
Ad26.COV2.S	Pulmonary embolism	68/M	7[c]	Unresolved	2/N	No
Ad26.COV2.S	Pulmonary embolism	54/M	45	Resolved	3/Y	No
Ad26.COV2.S	Pulmonary embolism	66/M	57	Unresolved	3/Y	No
Ad26.COV2.S	Transverse sinus thrombosis	25/M	21	Resolved	4/Y	No
Ad26.COV2.S	Cerebral infarction[b]	82/M	23	Resolving	4/Y	No
Ad26.COV2.S	Hemiparesis	49/F	28	Unresolved	1/Y	No
Ad26.COV2.S	Ischemic stroke[b]	82/M	41	Resolving	4/Y	No
Ad26.COV2.S	Myocardial infarction	70/M	12	Resolved	3/Y	No
Placebo	Deep vein thrombosis	57/M	3	Unresolved	2/N	No
Placebo	Deep vein thrombosis	44/M	6	Resolving	4/Y	Yes

Investigational Product	Adverse Event (PT)	Age/Sex	Day of Onset	Resolution Status	Grade/SAE[a]	Related[a]
Placebo	Pulmonary embolism	53/M	29	Resolving	4/Y	No
Placebo	Carotid artery occlusion	58/F	9	Resolving	4/Y	No
Placebo	Hemiparesis	45/M	9	Resolving	2/N	No
Placebo	Cerebrovascular accident	71/F	22	Unresolved	3/Y	No
Placebo	Acute myocardial infarction	78/M	3	Resolved	3/Y	No
Placebo	Acute myocardial infarction	52/F	4	Resolved with sequelae	4/Y	No
Placebo	Acute myocardial infarction	61/M	62	Fatal	4/Y	No
Placebo	Hemorrhoids thrombosed	42/F	24	Resolved	1/N	No

[a] Classification of events as SAEs and relatedness determined by study investigators
[b] Events occurred in the same study participant
[c] This event was initially reported with day of onset of 20 days. Day updated based on Sponsor clarification obtained on 2/17/21.

Additional details are provided for selected events among vaccine recipients for which a contributory effect of the vaccine could not be excluded based on FDA assessment of the clinical information provided:

- A 25-year-old male with no past medical history and no concurrent medications experienced a transverse sinus thrombosis on Day 21 following vaccination. On Day 9 the participant experienced symptoms of fever, myalgia, headache, fatigue, abdominal pain, congestion and rhinorrhea. He tested negative for SARs-CoV-2 during this acute illness. Aside from headache, his symptoms improved. On Day 19 he experienced a tonic colonic seizure. A CT scan without contrast demonstrated a cerebral hemorrhage. On Day 21, a transverse sinus thrombosis was reported on a venogram. The participant underwent a thrombectomy as well as stent placement for stenosed right sigmoid sinus on Day 22. On Day 23 repeat venogram showed the presence of a new clot in the transverse sinus. A second thrombectomy with venoplasty was performed. Treating clinicians reported observing rapid thrombus formation during the two thrombectomy procedures that was consistent with a clinically hypercoagulable state. In their assessment, the transverse sinus thrombosis most likely occurred days before the participant's clinical presentation with a seizure; the seizure was reported to be a consequence of a secondary bleed caused by elevated venous pressure from the venous flow obstruction. Workup for hematologic and infectious causes of the thrombosis did not reveal an etiology. This event was initially thought to be related to the study product by the investigator and prompted a study pause. After thorough investigation and expert consultation no clear cause of the event was identified; however possible contributing factors, such as preceding infection and an anatomical anomaly, were suggested. The investigator's brochure and informed consent form were updated accordingly, and the study pause was lifted. The investigator and Sponsor's final assessment of this event was that it was not related to the study product.

- A 30-year-old female with hypothyroidism, obesity (body mass index: 36.5 kg/m^2), headaches, anxiety and depression and use of multiple medications including medroxyprogesterone, experienced a pulmonary embolism on Day 3 following vaccination. The participant was hospitalized following a syncopal episode and CT scan of the chest demonstrated an occlusive thrombus in a pulmonary artery. Treating clinicians attributed the

pulmonary embolism to hypercoagulability due to medroxyprogesterone acetate birth control. The event was not considered related to the study product by the investigator or the Sponsor. The last date of medroxyprogesterone acetate is not recorded.

- A 52-year-old male with obesity (body mass index: 32.4 kg/m^2) experienced a deep vein thrombosis (DVT) on Day 27 following vaccination. The participant experienced calf pain following physical activity on Day 13. An ultrasound on Day 27 demonstrated a DVT in a vein of the left calf. The event was considered non-serious by the investigator and related to the study product. The Sponsor considered the event not related to the study product.

- A 63-year-old male with type 2 diabetes, hypertension and osteoarthritis experienced a DVT on Day 23 following vaccination. The event was considered non-serious and not related to the study product by the investigator.

- A 49-year-old female with no past medical history and medication use including medroxyprogesterone experienced hemiparesis on Day 28 following vaccination. The event was considered serious by the investigator. No laboratory or imaging results were reported. The event was unresolved and ongoing on Day 51. The event was not considered related to the study product by the investigator or the Sponsor.

Assessment of the cases above is confounded by the presence of risk factors in the individual participants. Nevertheless, given the numerical imbalance between vaccine and placebo recipients and temporal relationship, vaccine cannot be excluded as a contributing factor. As such, data at this time are insufficient to determine if there a causal relationship between the vaccine and thromboembolic events. FDA will recommend surveillance for further evaluation of thromboembolic events with deployment of the vaccine into larger populations.

The SMQ for “convulsions” in the FAS demonstrated a numerical imbalance, with single events in 4 vaccine recipients and 1 event in a placebo recipient. All of the convulsion events reported by the vaccine recipients occurred within 28 days of vaccination. Two events in the vaccine groups were considered serious. Of the two serious events, one event was discussed above and occurred secondary to a cerebral hemorrhage in a participant with a transverse sinus thrombosis. The other serious event and one of the non-serious events occurred in participants with a history of seizures. FDA’s assessment is that these events are unlikely related to the study vaccine.

The SMQ for “hearing and vestibular disorders” included the PT “tinnitus” for which was a numerical imbalance was observed across treatment groups. Tinnitus was reported in 6 vaccine recipients (6 events) compared to no placebo recipients. Events of tinnitus are summarized in the table below.

Table 30. Tinnitus in Vaccine Recipients, Full Analysis Set, Study 3001

Investigational Product	Age/Sex	Day of Onset	Resolution Status	Grade/ SAE[a]	Possible Risk Factor(s)	Related[a]
Ad26.COV2.S	58/M	1	Resolving	1/N	Hypertension	No
Ad26.COV2.S	63/F	1	Resolved	1/N	Hypothyroidism	Yes
Ad26.COV2.S	25/F	2	Resolved	1/N	Allergic rhinitis, medication use	Yes
Ad26.COV2.S	51/M	12	Unresolved	1/N	Hypertension, hypothyroidism, medication use	No
Ad26.COV2.S	54/M	17	Resolving	1/N	Allergic rhinitis	No
Ad26.COV2.S	65/F	22	Resolving	2/N	History of tinnitus	No

[a] Classification of events as SAEs and relatedness determined by study investigators

An additional event of tinnitus was reported in the clinical development of Ad26.COV2.S. The event, reported in Study 1002, occurred in 21-year-old male with no reported past medical history and no concomitant medications who experienced sudden hearing loss on Day 34 post-vaccination with Ad26.COV2.S. The hearing loss was associated with tinnitus and blocked ear sensation. Testing revealed sensorineural hearing loss. Workup for etiology including laboratory tests and imaging did not reveal an etiology. Hearing improved and the event was resolved by Day 69. The event was not considered related to the study product by the investigator or the Sponsor.

Assessment of these cases is confounded by the presence of risk factors in the individual participants. As such, data at this time are insufficient to determine if there a causal relationship between the vaccine and tinnitus.

The SMQ for “angioedema” in the FAS demonstrated a numerical imbalance, with events reported among 0.2% of vaccine recipients (44 events in 44 participants) compared to 0.12% of placebo recipients (28 events in 27 participants). By PT, “urticaria” was reported in 8 vaccine recipients compared to 3 placebo recipients. Within 7 days of vaccination, 5 events occurred in the vaccine group and 1 event occurred in the placebo group, all of which were grade 1 or 2. Based on temporal association and biologic plausibility, FDA’s assessment is that the events of urticaria are possibly related to study vaccine.

The PT “wheezing” was reported in 12 vaccine recipients (0.05%) and 7 placebo recipients (0.03%). However, there was no meaningful imbalance in events within 7 days of vaccination, with 4 events occurring each group; one event in the placebo group was grade 3 and all others were grade 1 or 2.

The SMQ for “arthritis” in the FAS demonstrated a numerical imbalance, with events reported among 0.5% of vaccine recipients (110 events in 109 participants) compared to 0.36% of placebo recipients (83 events in 78 participants). By PT, “arthralgia” was reported in 91 vaccine recipients (92 events) compared to 62 placebo recipients (67 events). In vaccine recipients, 56 of these events (60.8%) occurred within 7 days following vaccination compared to 24 events (35.8%) in placebo recipients. FDA’s assessment is that these events likely represent vaccine reactogenicity.

The SMQ for “peripheral neuropathy” in the FAS demonstrated a numerical imbalance, with events reported among 0.21% of vaccine recipients (47 events in 45 participants) compared to 0.16% of placebo recipients (36 events in 35 participants). By PT, “muscular weakness” was reported by 31 vaccine recipients compared to 18 placebo recipients. In vaccine recipients, 18

of these events (58.1%) occurred within 7 days following vaccination compared to 6 events (33.3%) in placebo recipients. FDA's assessment is that these events likely represent vaccine reactogenicity.

Immediate Adverse Events

Immediate unsolicited reactions occurring within 30 minutes of vaccination were infrequent and occurred in 0.2% of participants in both the vaccine and placebo groups. There were no reports of anaphylaxis immediately following vaccination.

Serious Adverse Events

Deaths

As of January 22, 2021, 19 deaths were reported (3 vaccine, 16 placebo). Two deaths in the vaccine group were secondary to respiratory infections not due to COVID-19. A 61-year-old participant died of pneumonia on Day 24 following onset of symptoms on Day 13. A 42-year-old participant with HIV died on Day 59 following diagnosis of a lung abscess on Day 33. A 66-year-old participant died of unknown causes after waking up with shortness of breath on Day 45. The placebo recipients died of pneumonia (n=2), suicide (n=1), accidental overdose (n=1), myocardial infarction (n=1), malaise (n=1), unknown cause (n=3) and confirmed COVID-19 (n=6). An update on deaths reported from the time period of January 22 to February 5 included an additional 6 deaths. Of these 6 deaths, 2 occurred in the vaccine group and 4, including 1 due to COVID-19, occurred in the placebo group. None were related to the study product.

Non-fatal Serious Adverse Events

The proportions of participants who had at least one SAE reported through January 22, 2021 were 0.4% in the vaccine group and 0.4% in the placebo group. The most commonly reported SAE was appendicitis occurring in 6 vaccine recipients and 5 placebo recipients. There were no significant numerical imbalances in SAEs by preferred term.

Seven SAEs occurring in 7 vaccine recipients and 3 SAEs occurring in 2 placebo recipients were assessed by the investigator as related to study vaccination (Table 31). Of the 7 SAEs in the vaccine group, the Sponsor assessed 3 as related/likely related, 2 as possibly related, 2 as unrelated to the vaccine.

Table 31. SAEs Considered Related by Investigator, Full Analysis Set, Study 3001

Investigational Product	SAE (PT)	Age/Sex	Day of Onset	Resolution Status	Grade	Related (Sponsor Assessment)
Ad26.COV2.S	Radiculitis brachial	30/M	1	Unresolved	3	Yes (Reassessed as injection site pain)
Ad26.COV2.S	Post-vaccination syndrome	35/M	2	Resolved	3	Yes (Reassessed as reactogenicity)
Ad26.COV2.S	Facial paralysis	62/M	3	Resolving	2	No
Ad26.COV2.S	Vaccination site hypersensitivity	42/M	3	Resolved	3	Likely
Ad26.COV2.S	Facial paralysis	43/M	16	Resolving	2	No
Ad26.COV2.S	Guillain-Barre Syndrome	60/F	16	Unresolved	4	Possibly
Ad26.COV2.S	Pericarditis	68/M	17	Resolved	4	Possibly
Placebo	Deep vein thrombosis	44/M	6	Resolving	4	Indeterminate

Investigational Product	SAE (PT)	Age/Sex	Day of Onset	Resolution Status	Grade	Related (Sponsor Assessment)
Placebo	Epstein-Barr infection[a]	69/M	14	Resolved	3	No
Placebo	Atrial flutter[a]	69/M	21	Resolving	3	No

[a] Events occurred the same study participant

In FDA's opinion following review of narratives, the following 3 SAEs in the vaccine group are considered likely related to the study vaccine:

- A 42-year-old male with no personal or family history of allergic reactions experienced diffuse urticaria beginning on Day 3 following vaccination accompanied with systemic symptoms of fatigue, myalgia and arthralgia. Over the following two days the urticaria progressed, and the participant experienced angioedema of the lips as well as the sensation of itchy and tight throat, but no hypoxia or respiratory distress. The event did not meet Brighton Criteria for anaphylaxis. FDA's assessment is that this event was likely a hypersensitivity reaction to the study vaccine.

- A 30-year-old male was reported to have "brachial neuritis following vaccination" (PT: "radiculitis brachial") with pain at the site of vaccine administration on Day 1 which persisted and worsened over several days and was unresponsive to non-prescription analgesics. Evaluation included electroconductive studies, which revealed intact nerves with no denervation of the evaluated muscles, and MRI of the cervical spine, which did not reveal an etiology of the participant's symptoms. FDA's assessment of this event is that the pain at injection site is likely related to vaccination, however the diagnosis of brachial neuritis is unlikely given the findings on electroconductive studies.

- A 35-year-old male experienced generalized malaise, weakness, myalgia, shortness of breath, headache, sensation of numbness and tingling in upper extremities, chest pain and fever beginning on Day 2 following vaccination. The participant was hospitalized for exacerbated generalized weakness. Abnormal vital signs included fever (39.4°C), blood pressure (129/103 mmHg), heart rate (112bpm) and respiratory rate (19 breaths per minute). There was no hypoxia. On exam he complained of diffuse tenderness in the extremities. No abnormalities were noted on neurologic exam which included normal reflexes. Abnormal laboratory findings included a mild elevation of creatine kinase attributed to mild myositis. Laboratory testing was negative for COVID-19, influenza and RSV. Symptoms resolved by Day 4. FDA's assessment of this event is that it is likely systemic reactogenicity related to the study vaccine.

For the SAE of pericarditis, as no alternative etiology was determined, FDA's assessment is that the possibility that the vaccine contributed to the event cannot be excluded. Review of Janssen's safety database including all Ad26-based vaccines did not reveal any additional reports of pericarditis.

Reports of facial paralysis (Bell's Palsy) were overall balanced between vaccine and placebo recipients (2 vaccine, 2 placebo). In addition to the 2 SAEs of facial paralysis presented in Table 31 above, a third event in a 54-year-old vaccine recipient occurred on Day 19, described as facial swelling and "droopiness" with no facial asymmetry and intact cranial nerves II-XII. This event was not considered related by the investigator. In FDA's assessment, description of this event is not consistent with facial paralysis. Two events of facial paralysis were reported in placebo recipients on Days 2 and 29.

There were single reports of Guillain-Barre Syndrome (GBS) in a 60-year-old vaccine recipient and a 75-year-old placebo recipient occurring on Days 16 and 10, respectively. The event in the vaccine group was preceded by symptoms of chills, nausea, diarrhea and myalgia. In FDA's assessment the events of facial paralysis and GBS are unlikely related to study vaccine but a causal relationship cannot be definitively excluded.

Subgroup Analyses

With the exception of more frequent, generally mild to moderate reactogenicity in participants 18-59 years of age, there were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to vaccination. Participants were excluded if they were pregnant or planned to become pregnant within 3 months of vaccine administration. The study is collecting outcomes for all reported pregnancies in study participants.

Eight pregnancies were reported through January 22, 2021 (4 vaccine, 4 placebo). In 7 participants (3 vaccine, 4 placebo) vaccination was within 30 days after last menstrual period (LMP) and in 1 vaccine recipient vaccination was prior to LMP. Unsolicited AEs related to pregnancy include spontaneous abortion (1 vaccine, 0 placebo), incomplete abortion (0 vaccine, 1 placebo), elective abortion (0 vaccine, 2 placebo) and ectopic pregnancy (1 vaccine, 0 placebo). Among participants in the vaccine group, two pregnancies are ongoing with outcomes unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of Ad26.COV2.S in rabbits was submitted to FDA on January 19, 2021. FDA review of this study concluded that Ad26.COV.S given prior to mating and during gestation periods at dose of $1x10^{11}$ vp (2 times the human dose) did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal development.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the Ad26.COV2.S vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=43,783; 21,895 vaccine, 21,888 placebo) meets the expectations for efficacy in FDA's guidance for industry Development and Licensure of Vaccines to Prevent COVID-19 (June 2020). A subset of participants (N=6,736) was followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. The demographic and baseline characteristics of the all-enrolled population and the safety subset were similar with respect to age and sex but had imbalances with respect to race, baseline comorbidities, SARS-CoV-2 serostatus and geographic distribution.

Local site reactions and systemic solicited events among vaccine recipients were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (48.6%), headache (38.9%), fatigue (38.2%) and myalgia (33.2%); 0.7% and 1.8% of local and

systemic solicited adverse reactions, respectively, were reported as grade 3. Overall, solicited reactions were reported more commonly in younger participants.

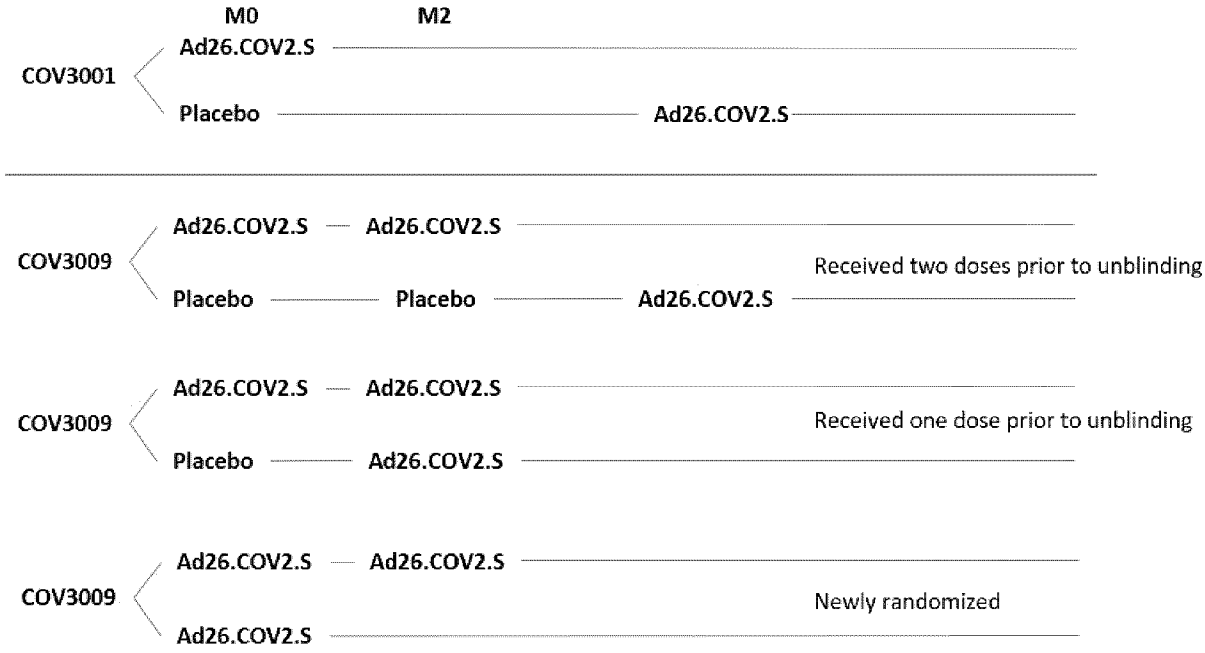
There were no meaningful imbalances in unsolicited adverse events in 28 days following vaccination between vaccine and placebo recipients in the safety subset. Among all adverse events collected through the data cutoff of January 22, 2021, a numerical imbalance was seen in urticaria events reported in the vaccine group (n=5) compared to placebo group (n=1) within 7 days of vaccination which is possibly related to the vaccine. Numerical imbalances were reported between vaccine and placebo recipients for thromboembolic events (15 versus 10) and tinnitus (6 versus 0). Based on currently available information, a contributory effect of the vaccine could not be excluded, although the imbalance was small (representing a difference of 0.06% of vaccine recipients vs. 0.05% of placebo recipients), and many of the participants had predisposing conditions. FDA will recommend surveillance for further evaluation of thromboembolic events with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events that would suggest a causal relationship to Ad26.COV2.S.

As of February 5, 2021, a total of 25 deaths were reported in the study (5 vaccine, 20 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups and include 7 deaths in the placebo group due to COVID-19 infection. Non-fatal serious adverse events, excluding those due to COVID-19, were infrequent and balanced between treatment groups with respect to rates and types of events (0.4% in both groups). A serious event of a hypersensitivity reaction, not classified as anaphylaxis, beginning 2 days following vaccination was likely related to receipt of the vaccine.

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

In the event that the Ad26.COV2.S vaccine receives FDA authorization for emergency use, the Sponsor proposes to submit a protocol amendment to Study 3001 that would allow all participants who received placebo to receive the vaccine (Figure 2). This would effectively result in unblinding of participants and investigators. However, participants who crossover from placebo will be encouraged to remain in the study up to 2 years after vaccination so that they may be followed for efficacy/effectiveness, safety, and immunogenicity. The Sponsor anticipates that open-label crossover vaccination would also be offered to placebo recipients in the ongoing Phase 1 and 2 studies. Janssen also proposes offering a single dose of Ad26.COV2.S to enrolled participants who initially received two doses of placebo in study COV3009. Because the study is expected to still be enrolling, participants who received a first dose of placebo will receive a dose of Ad26.COV2.S as their second dose and participants yet to be enrolled will be randomized to either a single-dose or a two-dose schedule of Ad26.COV2.S. Crossover vaccination would be made available to U.S. participants as soon as operationally feasible following the issuance of an EUA. Study investigators will be encouraged to consider current local public health guidance for determining the scheduling priority of participants.

Figure 2. Sponsor's Proposed Crossover Design Following Issuance of an EUA



7. Pharmacovigilance Activities

Janssen submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with the Janssen COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (including vaccine-associated enhanced respiratory disease), anaphylactic reactions (including anaphylaxis), and thromboembolic events as Important Potential Risks.

Important Missing Information includes: use during pregnancy and lactation, use in immunocompromised patients, use in patients with autoimmune or inflammatory disorders, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, and cardiovascular disorders), interaction with other vaccines, long-term safety, and use in pediatrics.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Serious adverse events (regardless of attribution to vaccination)
- Multisystem inflammatory syndrome
- COVID-19 disease resulting in hospitalization or death

The Sponsor will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- A narrative summary and analysis of vaccine administration errors whether or not associated with an adverse event, that were identified since the last reporting interval

- Safety concerns newly identified in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to fact sheets given to vaccination providers, changes made to studies, or studies initiated)

The Sponsor plans to conduct long-term follow-up of participants in the ongoing clinical trials. The Sponsor has also submitted protocols for the post-authorization studies listed below. FDA is reviewing the protocols and will provide feedback.

Pregnancy study: multi-country, observational, prospective cohort study of pregnant women vaccinated with Ad26.COV2.S to assess obstetric, neonatal, and infant outcomes

Active surveillance study of safety: retrospective, observational, propensity-scored matched cohort study using health insurance claims and electronic health records to assess the risk of prespecified adverse events of special interest following vaccination with Ad26.COV2.S

Active surveillance study of effectiveness: retrospective, observational propensity-scored matched cohort study using health insurance claims and electronic health records to estimate the effectiveness of Ad26.COV2.S to prevent medically attended COVID-19 in individuals vaccinated according to national immunization recommendations

Reporting to VAERS and Janssen

Providers administering the Ad26.COV2.S vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to the extent feasible, report to Janssen, the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (regardless of attribution to vaccination)
- Multisystem inflammatory syndrome
- COVID-19 disease resulting in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as V-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys to help COVID-19 vaccine recipients monitor for and report side effects. The system also will provide telephone follow-up to anyone who reports medically important adverse events. Responses indicating missed work, inability to do normal daily activities, or receipt of care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after vaccination
- Reduction in the risk of confirmed severe COVID-19 (including reduction in the risk of COVID-19 requiring medical intervention) occurring at least 14 days after vaccination

The vaccination regimen was effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the vaccine. The vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and for more severe disease, including COVID-19 requiring medical intervention, considering all cases starting 14 days after vaccination. Efficacy findings were also generally consistent across evaluable subgroups, including by age, race, ethnicity, and risk for severe COVID-19. Although VE estimates appeared to be lower in the subgroup of participants 60 years of age and older with comorbidities, an increase in VE estimates and narrowing of the CI was observed with inclusion of more cases (i.e., starting at 14 days post-vaccination and cases not yet centrally confirmed), indicating that the results seen potentially reflect imprecision associated with smaller numbers of cases. Additionally, case splits for COVID-19 requiring medical attention among participants 60 years of age and older with comorbidities further support benefit of the vaccine in this subgroup. Although a lower efficacy overall was observed in South Africa, where there was a predominance of B.1.3.5 lineage during the time period of this study, vaccine efficacy against severe/critical COVID-19 was similarly high across the United States, South Africa, and Brazil.

The vaccine is administered as a single dose, which provides operational benefits to mass vaccination campaigns.

8.2 Unknown Benefits/Data Gaps

Duration of protection

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

Effectiveness in certain populations at higher risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the Ad26.COV2.S for individuals with prior infection with SARS-CoV2, there were limited cases of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. The study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available from participants ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of September 21, 2020 to January 22, 2021, in sites across the United States, South Africa, and 6 countries in Latin America, which was a setting of high disease incidence with several regionally circulating SARS-CoV-2 variants. The evolution of the pandemic characteristics, including potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the

effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Available Day 71 N-serology data from a small subset of participants in the study, with infrequent evaluations of serological and virological measurements, are limited to assess the effect of the vaccine in preventing asymptomatic infection. There is uncertainty about the interpretation of these data and definitive conclusions cannot be drawn at this time.

Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization and including additional data to support the sensitivity of serologic and virologic surveillance methods.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[8-11] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting 1 to 2 days. The most common solicited adverse reactions were

injection site pain (48.6%), headache (38.9%), fatigue (38.2%) and myalgia (33.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, were reported as grade 3. Overall, solicited reactions were reported more commonly in younger participants. Among all adverse events collected through the data cutoff of January 22, 2021, a numerical imbalance was seen in urticaria events reported in the vaccine group (n=5) compared to placebo group (n=1) within 7 days of vaccination with is possible related to vaccination. Numerical imbalances were also observed between vaccine and placebo recipients for thromboembolic events (15 versus 10) and tinnitus (6 versus 0), with many of the participants experiencing these events having predisposing risk factors. Data at this time are insufficient to determine a causal relationship between these events and the vaccine.

Serious adverse events, while uncommon (0.4% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs that occurred in the vaccine group, FDA considered 3 as related: hypersensitivity reaction, not classified as anaphylaxis (n=1), severe and persistent injection site pain (n=1), and severe systemic reactogenicity (n=1). For the serious adverse events of pericarditis, facial paralysis and GBS, data are insufficient to determine a causal relationship to vaccination.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

8.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals and their infants, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of Ad26.COV2.S in female rabbits concluded that Ad26.COV2.S given prior to mating and during gestation periods at dose of $1x10^{11}$ vp (2 times human dose) did not have any effects on female reproduction, fetal/embryonal development, or postnatal development.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial population of approximately 20,000 vaccine recipients over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

9. References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.
2. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England).* 2020;395(10224):565-574.
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e278.
5. Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011).
6. FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.
7. National Vaccine Injury Compensation Program. Vaccine Injury Table, Revised and Effective March 21, 2017. https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf.
8. Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group, the. Historical Comparisons of Morbidity and Mortality for Vaccine-Preventable Diseases in the United States. *JAMA.* 2007;298(18):2155-2163.
9. Verhees RAF, Dondorp W, Thijs C, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: Is a trial on mortality ethically acceptable? *Vaccine.* 2018;36(21):2991-2997.
10. Flannery B, Reynolds SB, Blanton L, et al. Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014. 2017;139(5):e20164244.
11. Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017-2018 Influenza Season. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(11):1845-1853.

10. Appendix A. Other Clinical Studies Ad26.COV2.S

10.1 Study 1001

Design: Study 1001 is an ongoing, randomized, double-blind, placebo-controlled, first-in-human Phase 1/2a study, conducted in Belgium and the United States in healthy adults ages 18 to 55 years and in adults ≥65 years in good health with and without stable underlying conditions. Participants are randomized to placebo or Ad26.COV2.S administered at either of two dose levels (5×10^{10} vp or 1×10^{11} vp) and either as a single dose or as 2 doses 56 days apart. The total study population will include 1,045 adults. By the cutoff date of January 11, 2021, the median follow-up time for participants in the 18 to 55 and ≥65 age groups were 166 and 144 days, respectively.

Objectives/Endpoints Relevant to the EUA: The primary objective is to assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels. In addition, immunogenicity of the Ad26.COV2.S regimens is being assessed. Humoral immunogenicity is assessed via SARS-CoV-2 neutralizing antibody response as measured by a wild type SARS-CoV-2 neutralization assay (wtVNA). Spike protein binding antibody responses after one vaccination are measured by S-ELISA. Cellular immunogenicity is measured by S-specific CD4+ and CD8+ T-cell responses. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Results: A single dose of Ad26.COV2.S at the 5×10^{10} vp dose level (the dose level selected for the Phase 3 studies) elicited a SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 Spike binding antibody response that was detected by Day 15 and is increased by the Day 57 timepoint. Ad26.COV2.S was able to elicit cellular responses in participants consistent with a Th-1 phenotype. Ad26.COV2.S, given as a single dose was found to have an acceptable safety and reactogenicity profile in adults ≥18 years of age and did not raise safety concerns in any of the assessed populations.

10.2 Study 1002

Design: Study 1002 is a randomized, double-blind, placebo-controlled Phase 1, non-US IND study being conducted in Japan. The study population is comprised of healthy adults ages 20 to 55 years and ≥65 years in good health with or without stable underlying conditions. The primary objective is to assess the safety and reactogenicity of Ad26.COV2.S at two dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM with a 56-day interval. The immunogenicity of the Ad26.COV2.S regimens is also being assessed.

Results: In an interim analysis (data cutoff October 3, 2020), a single dose of Ad26.COV2.S elicited SARS-CoV-2 neutralizing antibody responses in participants 20-55 years of age by Day 29 post-vaccination, consistent with results of Study 1001. Both dose levels had acceptable tolerability and no safety concerns have been identified.

10.3 Study 2001

Design: Study 2001 is a randomized, double-blind, placebo-controlled Phase 2a study being conducted in Germany, Spain, and the Netherlands in healthy adults ≥18 to ≤55 years of age and adults in good or stable health ≥65 years of age. The study will also include a cohort of adolescents ≥12 to ≤17 years of age (not yet enrolled). Adults receive placebo or Ad26.COV2.S

at one of four dose levels: 1×10^{11} vp, 5×10^{10} vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$. A target of approximately 550 adult participants will be enrolled, with approximately one third ≥65 years of age.

Objectives/Endpoints Relevant to the EUA: The study will evaluate the safety, reactogenicity, and humoral immune response of Ad26.COV2.S in 1- and 2-dose vaccination regimens followed by antigen presentation after 4 months (2-dose regimen) or 6 months (1-dose regimen).

Results: Ad26.COV2.S elicited SARS-CoV-2 neutralizing antibody responses by Day 29 post-vaccination, consistent to those of the Phase 1/2a Study 1001. No safety concerns have been identified in any of the assessed populations.

10.4 Study 3009

Design: Study 3009 is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 years of age being conducted in 10 countries. Participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection are randomized 1:1 to receive Ad26.COV2.S 5×10^{10} vp or placebo as 2-dose regimen with a 56-day interval. The objectives and endpoints are similar to those of Study 3001.

Results: Enrollment is ongoing. No safety concerns had been identified based on blinded reports of SAEs and deaths with a cutoff date of February 5, 2021.

11. Appendix B. Case Definitions for Mild COVID-19 and FDA Harmonized COVID-19

11.1 Case Definition for Mild COVID-19

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

AND at any time during the course of observation:

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

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

11.2 FDA Harmonized Case Definition for COVID-19

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

AND

- Any COVID-19 symptom: 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.