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

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

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

FDA Briefing Document

EUA amendment request for a booster dose for the Janssen COVID-19 Vaccine

Table of Contents

List of Tables

List of Figures

Glossary

AE	adverse event
AR	adverse reaction
ARDS	acute respiratory disease syndrome
CBER	Center for Biologics Evaluation and Research
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
COVID-19	coronavirus disease 2019
DVRPA	Division of Vaccines and Related Products Applications
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GBS	Guillain-Barré syndrome
GM	geometric mean
GMR	geometric mean ratio
GMT	geometric mean titer
HHS	Health and Human Services
ID50	50% inhibitory dose
IP	investigational product
ITP	immune thrombocytopenia
LLOQ	lower limit of quantification
LOD	limit of detection
MAAE	medically attended adverse events
MERS-CoV	Middle Eastern respiratory syndrome
NE	non-evaluable
OVRR	Office of Vaccines Research and Review
psVNA	pseudovirus neutralization assay
RWE	real-world evidence
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardized MedDRA Query
TEE	thromboembolic event
TTS	thrombocytopenia syndrome
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern
vp	virus particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee
wtVNA	wild type virus neutralization assay

1 Executive Summary

On February 27, 2021, FDA issued an Emergency Use Authorization for the Janssen COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The Janssen COVID-19 vaccine, also referred to 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 authorized primary vaccination is a single intramuscular injection of 5×10^{10} virus particles (vp).

On October 4, 2021, Janssen (the Sponsor) submitted a request to amend their EUA to include use of a booster dose (5×10^{10} vp) in individuals 18 years of age and older. Janssen's proposed interval between the primary vaccination and booster dose is: "A booster dose is recommended at 6 months or later, based on the strength of the immune responses, although a booster dose may be administered as early as 2 months."

To support their EUA amendment request, the Sponsor submitted analyses of data from four clinical trials (COV1001, COV1002, COV2001, and COV3009) that evaluated the safety and immunogenicity or efficacy of Ad26.COV2.S (5×10^{10} vp) either as a second dose administered in the range of 2-3 months after the first dose or as a booster dose administered approximately 6 months after a single-dose primary vaccination. To further support the benefit of a booster dose, the Sponsor also submitted final blinded, placebo-controlled efficacy analyses from their Phase 3 clinical trial evaluating the single-dose primary vaccination (COV3001, with longer-term follow-up than the analyses that supported the original EUA) and analyses of vaccine effectiveness from a real-world observational study of Janssen COVID-19 Vaccine used under EUA in the U.S. (COV4002). Corresponding datasets supporting analyses from the clinical trials (but not the real-world effectiveness study) were also included in the EUA amendment request. However, except for immunogenicity assessments of the 6-month booster dose interval in study COV1001, datasets were not submitted in sufficient time for FDA to conduct an independent review to verify the Sponsor's analyses. Thus, FDA's assessment of the Sponsor's submission is based on a review of Sponsor-generated analyses that FDA determined to be most relevant to the request for use of a booster dose of 5×10^{10} vp. The key analyses considered by FDA to support use of a Janssen COVID-19 Vaccine booster dose (5×10^{10} vp) are as follows:

<u>Effectiveness of single-dose primary vaccination</u>

- The final efficacy analyses from study COV3001, a randomized, double-blinded, placebo-controlled study that enrolled approximately 40,000 adult participants, suggest vaccine efficacy (VE) of 56.3% (95% CI: 51.3%, 60.8%) against molecularly confirmed moderate and severe/critical COVID-19 from 14 days following a single-dose primary vaccination with Ad26.COV2.S, and VE of 73.3% (95% CI: 63.9%, 80.5%) against molecularly confirmed severe/critical COVID-19 from 14 days following a single-dose primary vaccination with Ad26.COV2.S. Additional analyses suggest decreased protection against moderate and severe/critical COVID-19 with increased time since vaccination (estimate of 72% VE from 15-28 days post-vaccination vs. 42.2% VE from 113 days post-vaccination to exit from blinded follow-up), though these analyses did not suggest waning of protection against severe/critical COVID-19. Decreases in VE over time may be due at least in part to emergence of vaccine-resistant variants in some regions outside the U.S. where the study was conducted.

- Estimates of vaccine effectiveness from the real-world observational study, COV4002, are generally consistent with VE estimates from study COV3001 and do not suggest decreased protection over time or coincident with circulation of the Delta variant in the U.S.

- In analyses from both study COV3001 and COV4002, VE estimates for the single-dose Janssen COVID-19 vaccine primary vaccination are lower than those reported for two-dose mRNA COVID-19 vaccines.

Efficacy of two doses (5×10^{10} vp each dose) administered 56 days apart

- In study COV3009, an efficacy analysis of blinded, placebo-controlled follow-up (median of 36 days post-dose 2) among approximately 30,000 adult participants suggests a VE of 75.2% (95% CI: 54.6%, 87.3%) against molecularly confirmed moderate and severe/critical COVID-19 from 14 days post-dose 2 and a VE of 100% (95% CI: 32.6%, 100%) against molecularly confirmed severe/critical COVID-19 from 14 days post-dose 2 (estimated from only 8 cases in the placebo group and none in the vaccine group). In subgroup analyses of efficacy by country, the VE estimate against moderate and severe/critical COVID-19 in the U.S. was 93.7% (95% CI: 58.4%, 99.9%). The confidence interval for this U.S. VE estimate overlapped with that for the overall VE estimate post-dose 2 in study COV3009 and with the confidence interval for the U.S. VE estimate following a single dose from the final efficacy analyses in study COV3001 (VE estimate of 72.9%; 95% CI: 65.7%, 78.7%). Insufficient cases of COVID-19 caused by the Delta variant were identified to estimate VE post-dose 2 against this variant.

Immunogenicity of dose 2 (5×10^{10} vp) administered approximately 2-3 months after dose 1

- In studies COV1001, COV1002, and COV2001, the geometric mean increase in neutralizing antibody titers against the reference strain (Victoria/1/2020), as measured by a validated wild-type virus neutralization assay, at 14-28 days post-dose 2 was approximately 1.5- to 4-fold above the pre-dose 2 baseline. These analyses, which were limited by small sample sizes (N=~25-50 samples per time point), suggest that a 3-month interval may result in a more robust neutralizing antibody booster response than a 2-month interval.

Immunogenicity of a 5×10^{10} vp booster dose administered 6 months after primary vaccination

- In study COV1001, the geometric mean increase in neutralizing antibody titers against the reference strain (WA1/2020 with D614G mutation), as measured by an exploratory (non-validated) pseudovirus neutralization assay (psVNA) at 7 and 28 days post-booster, was 6.8-fold and 10.5-fold above the pre-booster baseline, respectively. The geometric mean increase in neutralizing antibody titers against the Delta variant, also as measured by an exploratory (non-validated) psVNA at 7 and 28 days post booster, was 2.2-fold and 3-fold above the pre-booster baseline, respectively. These analyses were limited by small sample sizes (N=15-17 samples per time point), and titers from 28 days post-primary vaccination and pre-boost timepoints suggest that the assay may have low sensitivity.

Safety of a second dose or booster dose (5×10^{10} vp)

- The safety database to support use of a booster dose comes primarily from study COV3009, with smaller contributions from studies COV1001, COV1002 and COV2001. The total number of exposed subjects is 8049. The analyses of reactogenicity data during the 7 days post-booster and the unsolicited AEs within 28 days post-booster do not appear significantly different from those for the single-dose primary vaccination and do not raise new safety concerns. The limitations of these data include the length of the follow-up (median of 36

days of blinded follow-up post-dose 2 in study COV3009) and limited safety data are available for a booster dose administered 6 months after the primary dose (N=17). While the overall size of the database (N=8049) may not be adequate to characterize infrequently occurring serious adverse events, the Sponsor has presented a plan (currently under review by FDA) to continue monitoring safety events following administration of a booster dose if authorization is granted.

This October 15, 2021 VRBPAC meeting is being held to discuss whether the data presented by Janssen support the safety and effectiveness of Janssen COVID-19 Vaccine for emergency-authorized use as a booster dose at least 2 months after a single-dose primary vaccination, and whether the data presented by Janssen support that an interval of at least 6 months between the primary vaccination and booster dose may result in a more robust booster response.

2 SARS-CoV-2 Virus and COVID-19 Disease

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. 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). 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). SARS-CoV-2 is the causative agent 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.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of September 7, 2021, has caused approximately 222 million cases of COVID-19, including 4.5 million deaths worldwide. In the United States, more than 42 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 85.5% have occurred in individuals 18 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2, and emerging variants (such as the highly transmissible Delta variant that is now predominant in the U.S.) have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

Following emergency use authorization of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. While recently reported cases appear to be declining relative to the Delta variant-associated peak globally and in the U.S., the future course of the pandemic is uncertain.

2.1 Vaccines Licensed for SARS-CoV-2

On August 23, 2021, FDA approved COMIRNATY (COVID-19 vaccine, mRNA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19.

2.2 Authorized Vaccines and Therapies for COVID-19

FDA has issued EUAs for three COVID-19 vaccines as shown in Table 1 below.

Table 1. Emergency Use Authorized Vaccines to Prevent COVID-19

Sponsor	Regimen	Population	Date of EUA and Amendments
Pfizer/ BioNTech	2 doses 3 weeks apart	Individuals ≥16 years of age Individuals ≥12 years of age	December 11, 2020 EUA Amendment: May 10, 2021
Pfizer/ BioNTech	3rd primary series dose at least 1 month after completing the primary series	Certain immunocompromised[a] individuals ≥12 years of age	EUA Amendment: August 12, 2021
Pfizer/ BioNTech	Booster dose at least 6 months after completing the primary series of Pfizer/BioNTech COVID-19 vaccine (COMIRNATY)	Individuals ≥65 years of age Individuals 18 through 64 years of age at high risk of severe COVID-19 Individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19	EUA Amendment: September 22, 2021
Moderna	2 doses 4 weeks apart	Adults ≥18 years of age	December 18, 2020
Moderna	3rd primary series dose at least 1 month after completing the primary series	Certain immunocompromised[a] individuals ≥18 years of age	EUA Amendment: August 12, 2021
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021

a. Individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Remdesivir is the only product currently approved by the FDA for use in adults and pediatric patients 12 years of age and older for treatment of COVID-19 requiring hospitalization. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients and remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure.

Emergency use authorizations of COVID-19 pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 are as follows:

Table 2. Emergency Use Authorized Pharmacological Products for Post-Exposure Prophylaxis and/or Treatment of COVID-19

Product	Date of EUA	Authorized Use and Population
SARS-CoV-2-targeting Monoclonal Antibodies		
• Bamlanivimab/etesevimab • Sotrovimab • Casirivimab/imdevimab	Reissued September 16, 2021 May 26, 2021 Reissued September 9, 2021	All three products are indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older at high risk for progressing to severe COVID-19[a]

Product	Date of EUA	Authorized Use and Population
		Casirivimab/imdevimab is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in patients at high risk for progressing to severe COVID-19[b]
Antiviral Drugs		
• Remdesivir	Reissued October 22, 2020 (following FDA approval in adults and some pediatric patients)	Treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg
Immune Modulators		
• Baricitinib	Reissued July 29, 2021	Treatment of COVID-19 in hospitalized patients[b] receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
• Actemra	June 24, 2021	
COVID-19 Convalescent Plasma	Reissued March 9, 2021	Treatment of hospitalized patients with COVID-19

a Indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kg
b Indicated for adults and pediatric patients 2 years and older
ECMO extracorporeal membrane oxygenation, EUA emergency use authorization
Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs Accessed August 2, 2021.

2.3 Emergency Use Authorization of Janssen COVID-19 Vaccine

On February 27, 2021, FDA issued an EUA for the Janssen COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The Janssen COVID-19 Vaccine, also referred to 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 vaccine is supplied as a multidose vial (5 doses, each 0.5 mL) containing a refrigerated suspension with a shelf life of 3 months when stored at 2º to 8º C and does not contain a preservative. The authorized regimen is a single intramuscular injection at the dose level of 5×10^{10} virus particles. Issuance of the EUA was based on a finding of vaccine efficacy (VE) of 66.9% compared to placebo against confirmed COVID-19 at least 14 days after vaccination and a favorable benefit/risk balance based on review of safety data from approximately 40,000 participants with a median follow-up of 2 months post-vaccination.

2.3.1 Efficacy of a Primary Dose of the Janssen COVID-19 Vaccine

Efficacy of the Janssen COVID-19 Vaccine for the prevention of COVID-19 with onset at least 14 days after vaccination and at least 28 days after vaccination (co-primary endpoints) was evaluated in an ongoing Phase 3 study in approximately 40,000 participants who were randomized 1:1 to receive intramuscular injections of vaccine ($5x10^{10}$ vp) or saline placebo. Four groups of participants were progressively enrolled by age (18-59 years or ≥60-years) and health risk (with or without comorbid conditions), with participants ≥60 years of age and participants with at least one comorbid condition comprising approximately 35% and 40% of the total study population, respectively. The co-primary efficacy analysis (data cutoff of January 22,

2021) included 39,321 randomized participants with a median follow-up time of 2 months post-vaccination in the blinded, placebo-controlled follow-up period.

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. Analyses of secondary endpoints estimated 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 at 76.7% (54.6, 89.1) and 85.4% (54.2, 96.9), respectively.

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 in the U.S.), 20H/501Y.V2 variant (B.1.351) in South Africa (94.5% of sequenced cases in South Africa), and variant of the P.2 lineage in Brazil (69.4% of sequenced cases in Brazil, with the remaining 30.6% Wuhan-H1 variant D614G).

2.3.2 Safety of a Primary Dose of the Janssen COVID-19 Vaccine

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

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 postvaccination.

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. An imbalance in the number of participants with thromboembolic events was observed between vaccine (14 participants with 15 events) and placebo (10 participants with 10 events). An imbalance was also observed for tinnitus with 6 events in 6 participants in the vaccine arm and no events in the placebo arm. Data at the time of the EUA review were 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 January 22, 2021 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.

2.3.3 Post-EUA Safety Surveillance

As of October 8, 2021, more than 15 million doses of the Janssen COVID-19 Vaccine have been administered in the U.S. Safety reports to VAERS following use of the Janssen COVID-19 Vaccine are summarized below. In general, VAERS data have limitations due to the passive and voluntary nature of VAERS reporting and full details of these events are not always available.

As of October 7, 2021, VAERS has received 62,844 reports (56,133 U.S. and 6,711 foreign). There were 12,699 serious non-fatal reports (of which there were 6,504 U.S. reports) and 1,367 deaths (of which there were 957 U.S. reports). The remaining 48,778 reports were non-serious events. The top ten most frequently reported MedDRA preferred terms (PTs) included: Headache (26.1%); Pyrexia (22.2%); Chills (18.6%); Fatigue (17.8%); Pain (16.8%); Nausea (13.5%); Dizziness (13.5%); Pain in extremity (10.0%); Myalgia (7.8%); Dyspnoea (6.7%).

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barré syndrome (GBS) are existing safety concerns that have been added to the Fact Sheets. Potential emerging safety concerns currently under evaluation include thromboembolic events (TEEs), myocarditis and pericarditis, and immune thrombocytopenia (ITP).

Thrombosis with thrombocytopenia syndrome (TTS): Post-authorization surveillance of VAERS identified reports of cerebral venous sinus thrombosis (CVST) and thrombosis with thrombocytopenia syndrome (TTS) after Janssen COVID-19 Vaccine. On 4/13/21, use of the vaccine in the US was paused because of concerns about a potential association with the vaccine. Upon review by the FDA, CDC, and the Advisory Committee on Immunization Practices, the pause was lifted on 4/23/21. The Fact Sheets were updated to include a Warning about TTS. As of 10/5/21, 47 cases of TTS have been confirmed after Janssen COVID-19 Vaccine based on expert adjudication with a standardized case definition. Evaluation of this safety issue is ongoing.

Guillain-Barré syndrome (GBS): Post-authorization surveillance of VAERS identified reports of Guillain-Barré syndrome (GBS). Based on review (not expert adjudication), the overall estimated observed-to-expected rate ratio was 4.18, corresponding to an absolute rate increase of 6.36/100,000 person-years.[1] The Fact Sheets were updated to include a Warning about GBS. Evaluation of GBS is ongoing.

Thromboembolic events (TEEs): Post-authorization surveillance of VAERS has identified a potential emerging safety concern for thromboembolic events (TEEs) with normal platelet counts. Venous thromboembolism (VTE) is described as an important potential risk in the PVP. As described in the Fact Sheets, section 6.1 *Clinical Trials Experience*, numerical imbalances, with more events in vaccine than placebo recipients, were observed for thromboembolic events (deep vein thrombosis; pulmonary embolism; transverse sinus thrombosis with thrombocytopenia). Recently, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) 27-30 September 2021 meeting concluded that there is a possible link to rare cases of venous thromboembolism (VTE) with Janssen COVID-19 Vaccine. For VTE, as per PRAC assessment, it is described that VTE has been observed rarely following vaccination with Janssen COVID-19 Vaccine and that the risk of VTE should be considered for individuals with increased risk factors for thromboembolism. FDA evaluation of TEE reports in VAERS is ongoing at this time.

Myocarditis and pericarditis: Post-authorization surveillance of VAERS has identified a potential emerging safety concern for myocarditis and pericarditis. Based on preliminary review (not including expert adjudication), the estimated observed-to-expected values were elevated for all adults 18 and older, with significant elevations in both sexes, numerous age strata, different risk windows, and different background rates. There were five deaths, all in people 30 or older and three in women. Evaluation of myocarditis and pericarditis is ongoing.

Immune thrombocytopenia: Post-authorization surveillance of VAERS has identified a potential emerging safety concern for immune thrombocytopenia (ITP). Based on preliminary review (not expert adjudication), the estimated observed-to-expected value is elevated. Evaluation of ITP is ongoing. Recently, the EMA PRAC 27-30 September 2021 meeting assessed cases of ITP following the Janssen COVID-19 Vaccine and AstraZeneca COVID-19 Vaccine and recommended updating the product information of both vaccines to include ITP. As per the PRAC assessment, cases of ITP have been reported within the first four weeks after receiving Janssen COVID-19 Vaccine and included serious cases with very low platelet counts.

3 Rationale For COVID-19 Vaccine Booster Doses

The recent emergence of the highly transmissible Delta variant of SARS-CoV-2 resulted in a new wave of COVID-19 cases in many parts of the world and has led to considerations for administration of booster doses to individuals who received primary vaccination in an effort to enhance immunity, and thus sustain protection from COVID-19.The Sponsor states that although their clinical efficacy study demonstrated that a single dose of Ad26.CVO2.S has conferred protection against severe/critical COVID-19 disease for at least 6 months post vaccination in adults (see Section 4 below), a decrease in protection over time against cases that include moderate COVID-19 was observed globally, which could be driven by waning protection or reduced efficacy against emergent SARS CoV-2 variants. Some real-world effectiveness studies have suggested declining efficacy of the Janssen COVID-19 Vaccine over time against symptomatic infection or against the Delta variant, while others have not. There are many potentially relevant studies, but FDA has not independently reviewed or verified the underlying data or their conclusions. Overall, data indicate that the Janssen COVID-19 Vaccine still affords protection against severe COVID-19 disease and death in the United States, although the highest effectiveness estimates (including for more severe COVID-19 disease) across clinical trials and real-world effectiveness studies evaluating the Janssen COVID-19 Vaccine are consistently less than the highest effectiveness estimates for the mRNA COVID-19 vaccines.

The expected benefit of booster vaccination will depend on the impact that booster vaccination has in reducing disease relative to the primary vaccination. Factors supporting authorization of a booster dose should consider the effectiveness of primary vaccination with the Janssen COVID-19 Vaccine over time and against circulating variants, the effectiveness (and its duration) of booster vaccination in preventing important COVID-19-related outcomes in individuals who have already received a primary vaccination, the dynamics of the pandemic in the United States, and the risks of booster vaccination in the general population or in certain subpopulations.

3.1 EUA Amendment Request for the Janssen COVID-19 Vaccine

On October 4, 2021, Janssen submitted a request to amend this EUA for the purpose of including the use of a booster dose of Ad26.COV2.S following a primary dose in individuals ≥18 years of age. The request is accompanied by analyses evaluating the safety and effectiveness

of a second dose of Ad26.COV2.S administered at intervals ranging from 2 to 6 months after the first dose in participants ≥18 years of age.

3.2 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)).[2]

- 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 in preventing, diagnosing, or treating such serious or life-threatening disease or condition that can be 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 authorize 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 the known and potential benefits of a booster dose outweigh the known and potential risks (see Sections 3.3 through 3.5 below).

In the event an EUA is issued for a booster dose of this vaccine, it would be considered unapproved and further investigation (under an Investigational New Drug Application) would continue.

3.3 FDA Guidance for Industry Related to COVID-19 Vaccines

To facilitate the manufacturing, clinical development, and licensure of COVID-19 vaccines, FDA published the guidance for industry entitled Development and Licensure of Vaccines to Prevent COVID-19 (June 2020) describing FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19.[3] This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines. The guidance notes that the efficacy of COVID-19 vaccines should be demonstrated in adequate and well controlled clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infection and/or disease. The guidance notes further that safety evaluations including the size of the database required to support licensure should be no different than for other preventive vaccines for infectious diseases. Of note, this guidance does not address immunogenicity studies to infer effectiveness of booster doses for COVID-19 vaccines. However, the guidance for industry document Emergency Use Authorization for Vaccines to Prevent COVID-19 (May 2021,

February 2021, originally issued October 2020) describes data needed to support the effectiveness of a modified COVID-19 vaccine against variants of concern (VOCs).[4] FDA has applied these concepts to effectiveness evaluations of booster doses afforded by the prototype vaccine (refer to Section 3.4 below).

3.4 Regulatory Considerations for a Booster Dose of COVID-19 Vaccines

The benefit of a booster dose must be weighed against potential risk. Available data should support the effectiveness of the booster dose, particularly against currently circulating SARS-CoV-2 variants, and benefit should be considered relative to the benefit provided by completion of the primary series. Safety data should be available to identify the most frequently reported adverse reactions associated with the booster dose. Pre-authorization clinical trials may not be adequately powered to characterize uncommon but potentially serious adverse reactions, such as TTS and GBS. It is currently not known if there will be an increased risk of these or other adverse reactions after a booster dose of the Janssen COVID-19 Vaccine. These risks and associated uncertainties have to be considered when assessing benefit and risk.

3.5 Data to Support an EUA Amendment for a Booster Dose of COVID-19 Vaccines

As noted above, the Guidance for Industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (May 2021) describes data that could support the effectiveness of modified COVID-19 vaccines directed against a variant of concern (VOC). While the current EUA amendment is not for a booster dose targeted to a VOC, the intended use in the current pandemic situation is analogous, and corresponding recommendations have been conveyed to product sponsors seeking discussions on booster dosing with the prototype vaccine, as summarized below.

Safety
Safety assessments, including solicited and local and systemic adverse events assessed daily for at least 7 days after each study vaccination as well as serious and other unsolicited adverse events assessed during the immunogenicity evaluation period, may be sufficient to support emergency use authorization of a booster dose. Evaluation in a larger safety database than initially planned for immunogenicity analysis may be warranted if safety signals that can be reasonably evaluated in pre-licensure/pre-authorization studies arise during clinical evaluation of the booster dose. Post-licensure/post-authorization studies should be conducted to assess longer-term safety for serious and other medically important adverse events.

Effectiveness
Effectiveness of a booster dose with a COVID-19 vaccine can be evaluated based on the efficacy of the manufacturer's authorized prototype vaccine made by the same manufacturing process and for which a clinical disease endpoint efficacy study has been conducted that met FDA's pre-specified success criteria. A determination of effectiveness of a booster dose should be supported by conducting clinical immunogenicity studies. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of a booster dose of COVID-19 vaccines. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (geometric mean titer and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by a booster dose vs. after completion of the primary series.

Clinical immunobridging studies should be conducted in which the prototype COVID-19 vaccine is administered to persons who previously received the prototype COVID-19 vaccine according to the authorized or licensed dose and dose regimen. The immune response induced by the booster dose should be compared to the immune response induced by the primary series, as assessed by neutralizing antibody seroresponse rates and GMTs against the original virus (reference strain) upon which the prototype vaccine was based. It is expected that the booster would induce an immune response against the reference strain and clinically relevant variants of concern at levels that meet or exceed those elicited by the primary series against the reference strain. The study should be adequately powered for primary immunogenicity analyses to demonstrate statistical immunobridging of seroresponse rate and GMT elicited by the booster dose compared to the primary series using immunobridging margins of -10% for seroresponse rates and 1.5-fold for GMTs, respectively.

Conducting immunobridging analyses and evaluating neutralization against clinically relevant variant viruses will require development of the appropriate neutralization assays specific for the purpose. These assays would need to be sufficiently characterized (e.g., sensitivity, specificity) as part of the qualification/validation process to understand and account for differences in behavior of the different input viruses (e.g., as a result of expressing different spike protein antigens) that could confound the ability to compare measured neutralization titers.

Risk/Benefit Assessment
A favorable benefit-risk assessment to support authorization or approval of a booster dose would depend on evidence that a booster dose is needed and evidence (i.e., immunogenicity data) that the booster dose would be effective not only against the original reference or prototype SARS-CoV-2 strain but also against circulating variants. Furthermore, it is expected that justification for the interval chosen for the booster dose is provided taking into account both safety and effectiveness considerations.

4 FDA Review of Clinical Safety and Effectiveness Data

4.1 Overview of Clinical Studies

This EUA amendment request includes analyses from 6 ongoing, randomized, controlled clinical trials, as well as one observational real-world effectiveness study, summarized in Table 3 below. Corresponding datasets supporting analyses from the clinical trials (but not the real-world-effectiveness study) were also included in the EUA amendment request. However, except where noted, datasets were not submitted in sufficient time for FDA to conduct an independent review to verify the Sponsor's analyses.

Updated final analysis results from study COV3001 describe vaccine efficacy of a single dose of Janssen COVID-19 Vaccine with a longer follow-up duration compared to the analysis performed at the time of the EUA review, and in the setting of different circulating variants (mainly outside of the US); these data are used by the Sponsor to justify the potential need for a booster dose. As the data cutoff for study COV3001 occurred prior to the surge in COVID-19 cases caused by the Delta variant, data from the real-world evidence study COV4002 is used to examine the efficacy of the Janssen COVID-19 Vaccine in the U.S. during a time when Delta was widely circulating.

To support the effectiveness of a booster dose given 6 months after the single-dose primary vaccination, Janssen submitted post hoc analyses of 17 participants in Study COV1001, which assessed as a secondary endpoint humoral immune response to Ad26.COV2.S measured by

neutralizing antibody titers against SARS-CoV-2. Additional immunogenicity data to support a booster dose at 6 months are expected to come from Study COV2008, which includes a substantially larger study population powered for prespecified immunobridging analyses that follow FDA guidance on data needed to support booster dose safety and effectiveness evaluations (described in Section 3.5, above). However, immunobridging analyses from this study were not included in Janssen's EUA amendment request and are not yet available.

Table 3. Key Clinical Studies Evaluating Ad26.COV2.S at a Dose Level of $5x10^{10}$ vp

Study Number[a]	Study Description	Regimen[b]	Sponsor Analyses Reviewed
COV3001	Phase 3 Efficacy, Immunogenicity, and Safety Study	Single Primary dose	Efficacy Safety
COV4002	Phase 4 Observational Study	Single Primary dose	Real World Evidence
COV3009	Phase 3 Efficacy, Immunogenicity, and Safety Study	2 doses with 2-month interval	Efficacy Safety
COV1001	Phase 1 Safety, Immunogenicity Study	2 doses with 2-, 3-, 6-month intervals	Immunogenicity Safety
COV1002 (non-IND Japan)	Phase 1 Immunogenicity Safety Study	2 doses with 2-, 3-month intervals	Immunogenicity
COV2001	Phase 2a Immunogenicity, Safety Study	2 doses with 2-, 3-month intervals	Immunogenicity

a ClinicalTrials.gov identifiers: COV1001=NCT04436276; COV1002=NCT04509947; COV2001=NCT04535453; COV2008=NCT04999111; COV3001=NCT04505722, COV3009=NCT04614948.
b Listed regimens are those that FDA considers relevant to the booster dose that the Sponsor is currently requesting; other dosing regimens evaluated in the studies but not considered relevant to the booster dose EUA request are not listed.

4.1.1 Analysis Populations

For studies COV1001, COV1002, and COV2001, the populations used for the analyses presented are defined in Table 4. Unless otherwise specified, the Per-Protocol Immunogenicity (PPI) Set is used when describing analyses pertaining to immunogenicity and the Full Analysis Set is used when describing analyses pertaining to safety.

Table 4. Analysis Populations

Population	Description
Full Analysis Set (FAS)[1]	All participants with at least one vaccine administration documented.
Per-Protocol Immunogenicity (PPI) Set[1]	All randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or from participants with natural infection occurring after screening (if applicable) will be excluded from the analysis set.

[1] Participants will be included in the treatment group to which they were randomly assigned.

For both COV3001 and COV3009, the primary efficacy analyses were performed on the Per Protocol Efficacy Set, which included all participants in the FAS who received the study vaccine (single dose for COV3001; 2 doses for COV3009) and who were seronegative at vaccination (at baseline for COV3001; at baseline and Day 71 for COV3009) and who had no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine.

4.1.2 Immunogenicity Assays

Neutralizing antibodies to SARS-CoV-2 Victoria/1/2020 strain (prototype strain) were measured using a qualified wild type virus neutralization assay (wtVNA) using the Victoria/1/2020 strain. Immunogenicity results displayed for COV1001-Cohorts 1a & 3, COV1002, and COV2001 are all based on the wtVNA.

For COV1001-Cohort 2a, immunogenicity against the reference strain was assessed with a pseudovirus neutralization assay (psVNA) using WA1/2020 strain with D614G mutation. Immunogenicity against the Delta variant was assessed with a psVNA using the B.1.617.2 lineage (Delta).

4.2 Study COV3001 Evaluating Primary Single Dose

4.2.1 Study 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 saline 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. The study is being conducted in 219 locations in the U.S., South Africa, and six countries in Latin America.

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. The COVID-19 case definitions used in this study are described in the EUA review memorandum for the Janssen COVID-19 Vaccine.[5]

4.2.2 Results from the Primary Analysis

Results from the primary analysis (cutoff date of January 22, 2021) are summarized in Section 2.3. See the Janssen COVID-19 Vaccine EUA review memo for further details on efficacy and safety from the primary analysis.

4.2.3 Final Vaccine Efficacy Analysis

The final analysis of the double-blind, placebo-controlled phase was performed when at least 90% of the study participants had been unblinded. Janssen submitted the final (updated) vaccine efficacy analyses for COV3001 to the EUA amendment. The median duration of double-blind, placebo-controlled follow-up for efficacy at the time of the July 9, 2021 data cutoff for the final analysis was 4 months. Approximately 23% of participants (4595 in the vaccine arm and 4345 in the placebo arm) had at least 6 months of double-blind, placebo-controlled follow-up.

A comparison of vaccine efficacy against the primary efficacy endpoint of centrally confirmed moderate and severe/critical COVID-19 based on data from the primary analysis (January 22, 2021 data cutoff used to support the initial EUA) and the final analysis (July 9, 2021 cutoff) is shown in Table 5. For ease of comparison, only the co-primary time point of onset of cases starting 14 days after vaccination is shown. The results based on cases with onset at least 28 days after vaccination is similar to the results based on onset at least 14 days after vaccination.

These efficacy analyses are summarized from topline results submitted by the Sponsor. FDA has not independently verified the data from the final efficacy analyses.

The vaccine efficacy point estimate decreased from 66.9% based on the January 22 cutoff to 56.3% at the July 9 cutoff. This decrease was also seen when assessing the efficacy for each of the two protocol-specified age cohorts. While this trend was consistent across the overall and age subgroup analyses, confidence intervals for the Primary Analysis and Final Analysis estimates overlapped.

Table 5. Vaccine Efficacy Against Centrally Confirmed Moderate and Severe/Critical COVID-19 With Onset at Least 14 Days After Vaccination, Primary Analysis and Final Efficacy Analysis, Study 3001, Per-Protocol Set (Analyses of July 9, 2021 Data Cutoff Not Verified by FDA)

	January 22, 2021 Data Cutoff			July 9, 2021 Data Cutoff		
Co-primary Endpoint Subgroup	**Ad26.COV2.S Cases (N)[a] Person-yrs[b]**	**Placebo Cases (N)[a] Person-yrs[b]**	**VE% (95% CI)**	**Ad26.COV2.S Cases (N)[a] Person-yrs[b]**	**Placebo Cases (N)[a] Person-yrs[b]**	**VE% (95% CI)**
All participants	116 (19514) 3116.6	348 (19544) 3096.1	66.9% (59.0, 73.4)	484 (19400) 6685.6	1067 (19398) 6440.18	56.3% (51.3, 60.8)
Age 18-59 years	95 (12750) 2106.8	260 (12782) 2095.0	63.7% (53.9, 71.6)	381 (12665) 4682.1	847 (12674) 4514.2	56.6% (51.0, 61.7)
Age ≥60 years	21 (6764) 1009.8	88 (6762) 1001.2	76.3% (61.6, 86.0)	103 (6735) 2003.5	220 (6724) 1926.0	55.0% (42.9, 64.7)

Source: Table 6, fa-tlr-vac31518cov3001.pdf
[a] N=Total number of participants at risk
[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.

A comparison of vaccine efficacy against severe/critical COVID-19, COVID-19 requiring medical intervention (defined as requiring hospitalization, ICU admission, mechanical ventilation, and/or ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings, and linked to molecularly confirmed COVID-19) and COVID-19-related deaths at the primary analysis and the final efficacy analysis is shown in Table 6. For these more severe endpoints, the VE point estimate appears to be similar between the two analyses, with narrower confidence intervals for the July 9, 2021 data cut-off resulting from the larger numbers of cases analyzed. No COVID-19-related deaths in the vaccine group were observed at the time of the primary analysis and three deaths in the vaccine group were observed at the time of the final analysis.

Table 6. Secondary Endpoints of Vaccine Efficacy Against Centrally Confirmed COVID-19 With Onset at Least 14 Days After Vaccination, Primary Analysis and Final Efficacy Analysis, Study 3001, Per-Protocol Set (Analyses of July 9, 2021 Data Cutoff Not Verified by FDA)

	January 22, 2021 Data Cutoff			July 9, 2021 Data Cutoff		
Secondary Endpoint	**Ad26.COV2.S N[a]=19514 Cases Person-yrs**	**Placebo N[a]=19544 Cases Person-yrs**	**VE% (95% CI)**	**Ad26.COV2.S N[a]=19400 Cases Person-yrs**	**Placebo N[a]=19398 Cases Person-yrs**	**VE% (95% CI)**
Severe/critical COVID-19	14 3125.1	60 3122.0	76.7% (54.6, 89.1)*	56 6774.6	205 6625.2	73.3% (63.9, 80.5)
COVID-19 requiring medical intervention	2 3125.9	8 3126.1	75.0% (-25.3, 97.4)	18 6783.9	74 6656.7	76.1% (56.9, 87.7)*
COVID-19 related deaths	0	5	Not calculated	3 6786.9	19 6668.4	84.5% (47.3, 97.1)

Source: Table 6, fa-tlr-vac31518cov3001.pdf
[a] N=Total number of participants at risk ; *adjusted CI

An exploratory analysis of VE stratified by time since vaccination was conducted based on data from the final analysis (Table 7). Results show a trend in decreasing VE against moderate and severe/critical COVID-19 with increasing time since vaccination, but this trend was not observed when only including severe/critical COVID-19 cases.

Table 7. Exploratory Analysis of Vaccine Efficacy Against Centrally Confirmed COVID-19 With Onset at Least 14 Days After Vaccination by Time Since Vaccination, Final Efficacy Analysis, Study 3001, Per-Protocol Set (Analyses Not Verified by FDA)

	Moderate and severe/critical COVID-19			Severe/critical COVID-19		
Time Point	Ad26.COV2.S Cases (N[a]) Person-yrs	Placebo Cases (N[a]) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N[a]) Person-yrs	Placebo Cases (N[a]) Person-yrs	VE% (95% CI)
Day 15-28	51 (19400) 1483.4	184 (19398) 1480.1	72.3% (62.1, 80.1)	10 (19400) 1484.1	29 (19398) 1482.9	65.5% (27.3, 85.0)
Day 29-56	119 (19113) 2877.4	306 (18924) 2837.4	61.7% (52.5, 69.2)	9 (19113) 2881.8	62 (18924) 2846.7	85.7% (71.0, 93.7)
Day 57-112	157 (17586) 5040.0	308 (17090) 4860.1	50.8% (40.2, 59.7)	18 (17586) 5051.6	54 (17090) 4882.0	67.8% (44.2, 82.2)
Day 113 to end DB Phase	157 (11379) 4900.4	265 (10572) 4529.3	45.2% (33.0, 55.3)	18 (11379) 4918.1	59 (10572) 4555.9	71.7% (51.4, 84.3)

Source: Table 10 and 11, fa-tlr-vac31518cov3001.pdf
[a] N=Total number of participants at risk

In an exploratory analysis of the primary efficacy endpoint (moderate and severe/critical COVID-19) that included only those cases that occurred in the U.S., (Table 8), VE appears to be stable over time, in contrast to a notable decrease in VE in the overall study population. The majority of cases from the U.S. were sequenced to be D614G, with some cases due to B.117 (Alpha) between February and April.

Table 8. Exploratory Analysis of Vaccine Efficacy Against Centrally Confirmed COVID-19 With Onset at Least 14 Days After Vaccination in United States, Primary Analysis and Final Efficacy Analysis, Study 3001, Per-Protocol Set (Analyses of July 9, 2021 Data Cutoff Not Verified by FDA)

	January 22, 2021 Data Cutoff			July 9, 2021 Data Cutoff		
Secondary Endpoint	Ad26.COV2.S N[a]=9119 Cases Person-yrs	Placebo N[a]=9086 Cases Person-yrs	VE% (95% CI)	Ad26.COV2.S N[a]=9057 Cases Person-yrs	Placebo N[a]=9002 Cases Person-yrs	VE% (95% CI)
Moderate and severe/critical	32 1414.9	135 1394.2	76.6% (65.5, 84.6)	93 2604.7	323 2453.7	72.9% (65.7, 78.7)
Severe/critical only	4 1417.2	14 1405.0	71.7% (9.8, 93.2)	11 2620.2	34 2511.9	69.0% (37.3, 85.8)

Source: Figure 8 and Figure 14, fa-tlr-vac31518cov3001.pdf
[a] N=Total number of participants at risk

Efficacy against variants

Multiple variants of SARS-CoV-2 were circulating during the conduct of study COV3001; these variants differed by country and changed over time. The final efficacy analysis was based on data from the double-blind phase of the study. Due to differences in availability and approval/authorization of COVID-19 vaccines, including the Janssen COVID-19 Vaccine, in the

countries where this study took place, the progression of unblinding varied among the study sites. In the U.S., the last available primary endpoint that contributed to the final efficacy analysis occurred on April 16, 2021.

Sequencing data at the time of the final analysis was available from 77.3% of subjects with molecularly confirmed COVID-19 cases. Of the sequenced cases, the most prevalent variants were P.1 (Gamma) at 12.8%, P.2 (Zeta) at 11.3%, B.1.351 (Beta) at 7.8%, and B.1.621 (Mu) at 6.5%. Only 2.3% of the cases sequenced were attributable to B.1.617.2 (Delta). As shown in Table 9, a post-hoc analysis of VE by variant showed a decrease in VE against the majority of variants of concern or interest as compared with the reference strain. However, for a majority of variants, the case numbers were small with wide confidence intervals around the efficacy point estimate. This analysis only accounted for cases which met the protocol definition of moderate to severe/critical and cases which occurred at least 14 days after vaccination in the per-protocol set. Thus, not all sequenced cases contributed to this exploratory efficacy analysis.

Table 9. Post-Hoc Analysis of Vaccine Efficacy Against Centrally Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 Days After Vaccination by Virus Variant, Final Efficacy Analysis, Study 3001, Per-Protocol Set (Analyses not Verified by FDA)

	Ad26.COV2.S N[a]=19400 Cases	Placebo N[a]=19398 Cases	VE% (95% CI)
Reference strain	32	108	71.5% (57.3, 81.4)
B.1.1.7 (Alpha)	9	29	70.1% (35.1, 87.6)
B.1.351 (Beta)	36	56	38.1% (4.2, 60.4)
B.1.617.2/AY.1/AY.2 (Delta)	11	10	-6.0% (-178.3, 59.2)
B.1.427/429 (Epsilon)	8	17	54.7% (-10.8, 83.1)
P.1 (Gamma)	74	112	36.4% (13.9, 53.2)
C.37 (Lambda)	43	46	10.0% (-39.5, 42.0)
P.2 (Zeta)	34	93	64.8% (47.3, 77.0)
B.1.621 (Mu)	38	57	35.8% (1.5, 58.6)

Source: Figure 6, fa-tlr-vac31518cov3001.pdf
[a] N=Total number of participants at risk

4.2.4 Safety Analyses

Updated safety analyses based on the July 9, 2021 data cutoff were submitted to the EUA amendment. The summary of safety analyses is based on topline summaries submitted by the Sponsor. FDA did not independently verify and analyze the updated safety data from study COV3001.

Rates of solicited local and systemic adverse events were similar to those of the primary analysis submitted to the initial EUA review.

The sponsor submitted an analysis of select adverse events of interest generated using Standardized MedDRA Queries (SMQs) for the entire double-blind follow-up period. The SMQ-

derived analyses continued to show an imbalance in categories noted during review of the EUA. For thromboembolic disorders, there were 40 (0.2%) events in the vaccine arm versus 36 (0.2%) events in the placebo arm. The difference is more pronounced for the Preferred Terms (PT) of deep vein thrombosis (11 in vaccine arm versus 3 in placebo arm) and pulmonary embolism (10 in vaccine arm versus 5 in placebo arm). Using the SMQ "Hearing and vestibular disorders," an imbalance was noted for the PT of tinnitus, with 15 events in the vaccine arm versus 4 events in the placebo arm. Using the SMQ "Convulsions," an imbalance was noted for the PT of seizure, with 7 events in the vaccine arm versus 2 events in the placebo arm.

In the double-blind phase, when excluding SAEs related to COVID-19, there were 223 SAEs (1.0%) SAEs observed in the vaccine arm versus 265 (1.2%) in the placebo arm. There were 19 SAEs in 18 participants assessed by the investigator as related to Ad26.COV2.S (Table 10). As narratives were not submitted with the EUA amendment, further details regarding these cases are not available, and FDA could not conduct an independent assessment of causality for these SAEs or for SAEs assessed by the investigator as unrelated to Ad26.COV2.S.

Table 10. SAEs Assessed as Related by Investigator After Ad26.COV2.S as of Data Cutoff Date (Data Not Verified by FDA)

Preferred Term	Age Group/Sex	Day of Onset Relative to Dose of Ad26.COV2.S	Outcome	AE Onset Relative to Unblinding
Asthma	18-59 F	1 (open-label)	Recovered	After
Complex regional pain syndrome	18-59 M	1	Not recovered	After
Post-vaccination syndrome	18-59 M	2	Recovered	Before
Bell's palsy	≥60 M	3	Recovered	Before
Hypersensitivity	18-59 M	3	Recovered	Before
Deep vein thrombosis	18-59 M	8 (open-label)	Not recovered	After
Guillain-Barre syndrome	≥60 F	16	Recovering	Before
Bell's palsy	18-59 M	16	Recovering	Before
Pericarditis	≥60 M	17	Recovered	Before
Ischemic stroke	≥60 M	17	Recovering	Before
Ischemic stroke	18-59 F	21 (open-label)	Recovered	After
Deep vein thrombosis	≥60 M	22	Recovered	Before
Headache	≥60 F	23 (open-label)	Recovered	After
Ischemic stroke	≥60 M	42 (open-label)	Recovering	After
Retinal vein thrombosis	≥60 M	50	Recovering	Before
Pulmonary embolism	18-59 M	57 (open-label)	Fatal	After
Pulmonary embolism; Venous thrombosis limb	≥60 F	149	Not recovered	After
Atrial fibrillation	18-59 M	182	Recovered	After

Source: Table 33, fa-tlr-vac31518cov3001.pdf

During the double-blind phase, there were 28 deaths reported in the vaccine arm versus 55 deaths in the placebo arm. When including the open-label phase of the study, there were a total of 40 deaths in the study which occurred in participants who received Ad26.COV2.S. Of the 14 deaths which occurred within 28 days after vaccination, 4 occurred after Ad26.COV2.S and 10 occurred after placebo. Regarding deaths which may be related to adverse events of interest, there were 3 deaths from pulmonary embolism among Ad26.COV2.S recipients (Day 57, Day 80, and Day 168 post-vaccination, respectively). In the placebo arm, there was one death from pulmonary embolism (Day 76 post-vaccination, in setting of COVID-19) and 3 deaths from

stroke or cerebrovascular accident (Day 79, Day 107, and Day 133 post-vaccination, respectively).

4.2.5 Study COV3001 Summary and Limitations

Vaccine efficacy against moderate and severe/critical COVID-19 decreased from 66.9% at the primary efficacy analysis (January 22, 2021 cutoff, median follow-up of 2 months) to 56.3% at the final analysis (July 9, 2021 cutoff, median follow-up of 4 months). Efficacy against severe/critical disease appears to have remained stable. There was also no notable decline in VE noted when considering only those COVID-19 cases which accrued in the United States. It is possible that the decreased overall VE was driven by decreased VE against variants that circulated in the countries where this study was conducted. An exploratory analysis of vaccine efficacy by variant in sequenced cases showed markedly decreased VE for certain variants, though the confidence intervals were wide. As the data cutoff for study COV3001 occurred prior to the Delta surge, an, insufficient number of cases due to the Delta variant occurred during the study to enable a determination of VE specifically against Delta. The efficacy analyses are summarized from topline results submitted by the Sponsor. FDA has not independently verified the data from the final analysis (July 9, 2021 data cutoff).

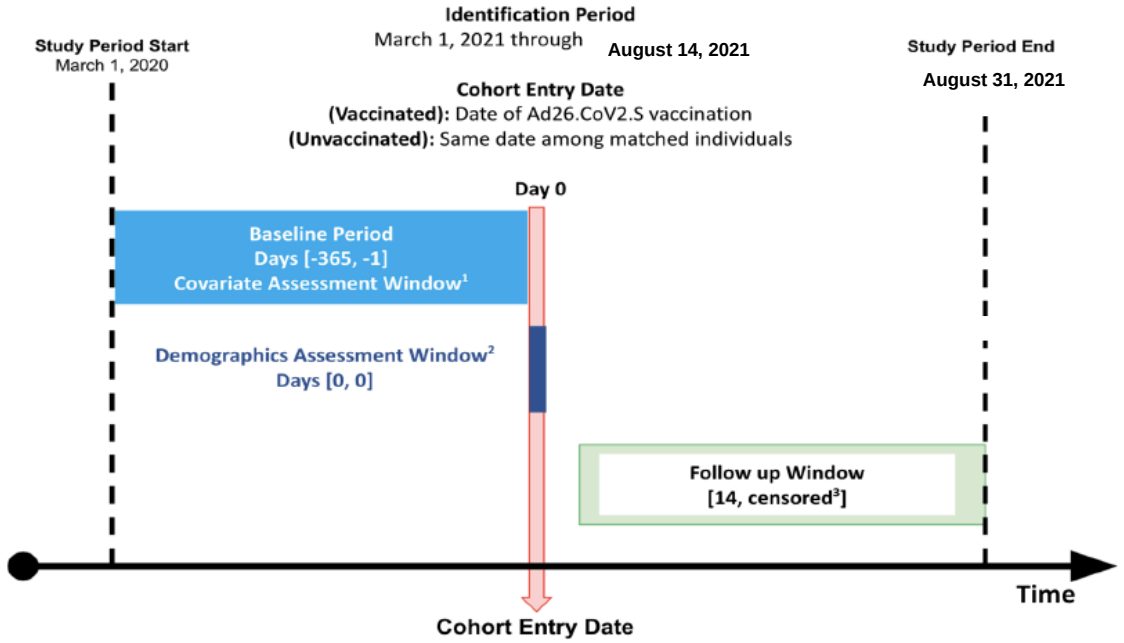
Safety analyses conducted at the time of the data cutoff showed similar signals as those observed at the time of the primary analysis. Adverse events of tinnitus, thromboembolic events, and seizures were more frequent in the vaccine arm compared to placebo. Out of the 19 SAEs assessed as related by the investigator, 9 were possible thromboembolic events (DVT, PE, stroke). The summary of safety analyses is based on topline summaries submitted by the Sponsor. FDA did not independently verify and analyze the updated safety data from study COV3001.

4.3 Real World Evidence Study Following a Primary Dose

4.3.1 Study Design

Study COV4002 aimed to estimate the effectiveness of Ad26.COV2.S after a single dose using real-world data from the Health Verity COVID-19 dataset. The data includes records from approximately 47.5 million individuals with multiple data sources including medical and pharmacy claims, hospital chargemaster records of inpatient and outpatient encounters, and laboratory data. Mortality is not reliably coded in any of the available data sources used in this study, and hence was not included in the outcome analysis. Individuals included in the final analytic dataset had at least 1 health care encounter in the prior 12 months as well as continued enrollment and pharmacy insurance before their index (cohort entry) date. A visual of the study design is displayed in Figure 1.

Figure 1. Design of Study COV4002



1 - Number of pharmacy/medical claims and comorbidities
2 - Age, sex and state
3 - Day 14 through observed endpoint or censoring

The vaccinated (treated) cohort was identified as those receiving Ad26.COV2.S in the identification period (starting March 1, 2021 and no later than August 17, 2021), with no documentation of any other COVID-19 vaccination in the 12 months prior to the start of the identification period. The final analysis included data up to August 31, 2021. The unvaccinated (referent) cohort is defined as those who have at least one claim for a healthcare interaction in the prior 12-months to the index date (date range of +/- 4 days of a treated individual's vaccination date) and have no documentation of any COVID-19 vaccine exposure. Treated and referent individuals were matched based on exact matches to time of exposure (index date), age (4-year age bins), sex and geography (3-digit zip codes).

A propensity score using logistic regression was estimated to further refine the matched vaccinated and unvaccinated cohorts to control for other covariates that may be associated with the risk and severity of COVID-19. Primary outcomes are defined as follows:

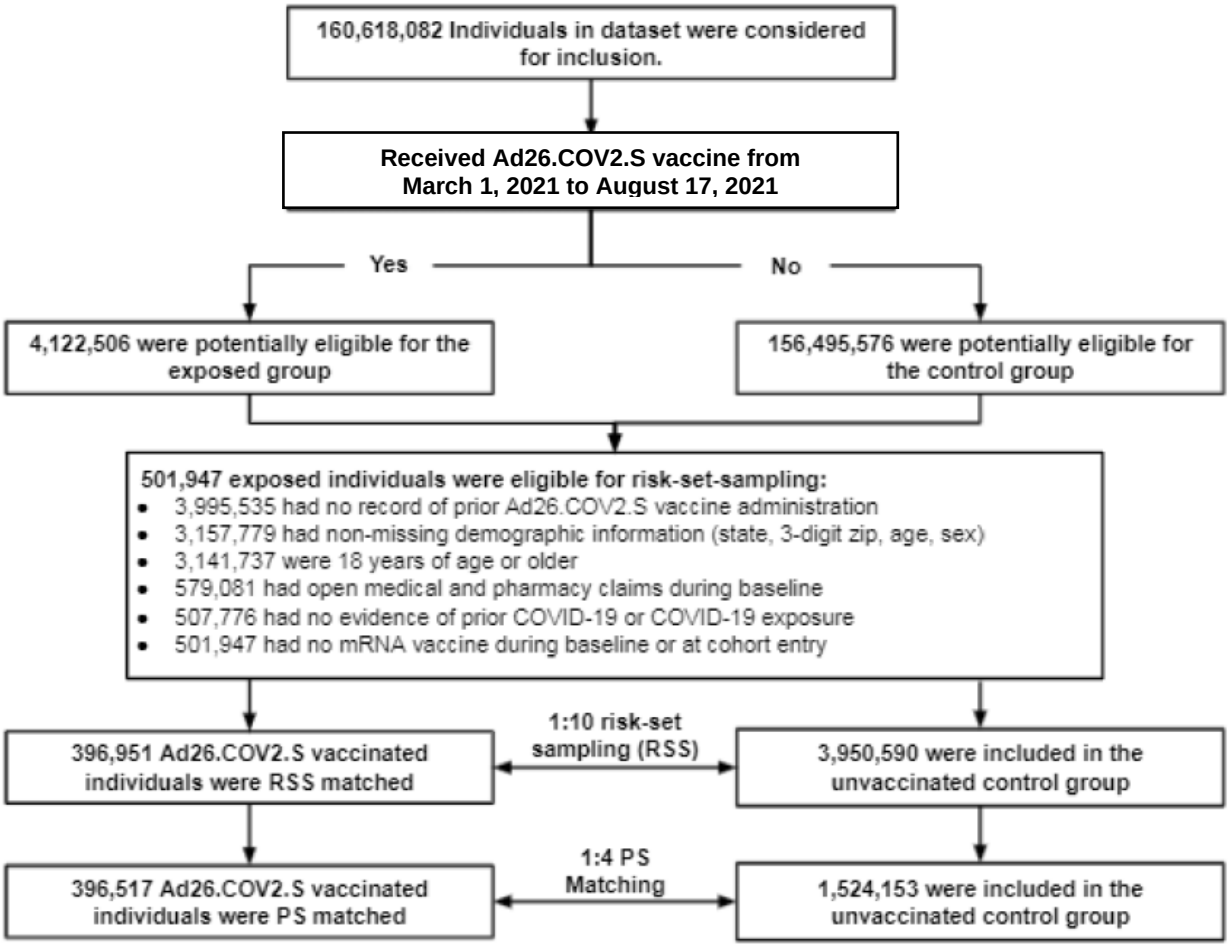
1. Any observed COVID-19 (positive SARS-CoV-2 test and/or diagnosis)
2. Occurrence of a COVID-19 hospitalization

Vaccine effectiveness (VE) for each of the outcomes of interest was estimated by using the hazard ratio (HR) from a Cox proportional hazards model and calculated as [(1-HR) x 100]. A sensitivity analysis was performed to assess the impact that under-ascertainment of vaccination status would have on VE.

Among the initial 160,618,082 patients in the Healthy Verity data, the final analysis set included 396,517 vaccinated individuals (those with a documented administration of one dose of

Ad26.COV2.S), and 1,524,153 unvaccinated individuals (see Figure 2 for attrition at each step described above).

Figure 2. Study COV4002 Population Consort Diagram



4.3.2 Vaccine Effectiveness

The final analytic cohort was well balanced across all measured covariates as assessed by the absolute standardized difference between the treated and referent cohorts. The median follow-up time up until the data cutoff (August 31, 2021) was 129 days.

Due to the difficulties in documentation of true vaccination status in the Health Verity COVID-19 dataset (vaccination may have been administered at facilities outside of those that would be captured in Health Verity, such as mass vaccination clinics), the Sponsor performed sensitivity analyses (Table 11) to correct VE estimates for the potential under-ascertainment of vaccination in the referent cohort. The sensitivity analyses resulted in VE estimates of any observed COVID-19 of 69% (67%, 71%) to 92% (91%, 92%). For the endpoint of COVID-19-related hospitalization, the sensitivity analyses produced VE ranging from 73% (74%, 76%) to 93% (92%, 94%). The shaded column of assumed 40% under-reporting represents the assumed adjustment factor for the “corrected” VE estimates throughout the RWE study. This correction

factor of 40% was based on the observation of vaccination rates seen in Health Verity in July 2021 (34%) and what was reported by CDC (57%), which amounts to ~41% fewer vaccinations observed in the RWE analytic dataset used for this study.

Table 11. Sensitivity Analyses for VE Assuming Varying Levels of Under-Ascertainment of Vaccination in the Referent Cohort (Analyses Not Verified by FDA)

	Percentage of Under-Reported Vaccination in the Referent Cohort				
	0%	**20%**	**40%**	**60%**	**80%**
Any observed COVID-19	69% (67%-71%)	73% (72%, 75%)	79% (77%-80%)	84% (83%, 85%)	92% (91%, 92%)
COVID-19 hospitalization	73% (69%, 76%)	77% (74%, 80%)	81% (79%, 84%)	87% (85%, 88%)	93% (92%, 94%)

VE numbers for any observed COVID-19 and COVID-19-related hospitalization endpoints included individuals in the study (national cohort) and by age (below 65, and 65 and older) and immunocompromised status are provided in Table 12

Table 12. Vaccine Effectiveness (Corrected and Uncorrected) for Select Cohorts from the RWE Study COV4002 (Analyses Not Verified by FDA)

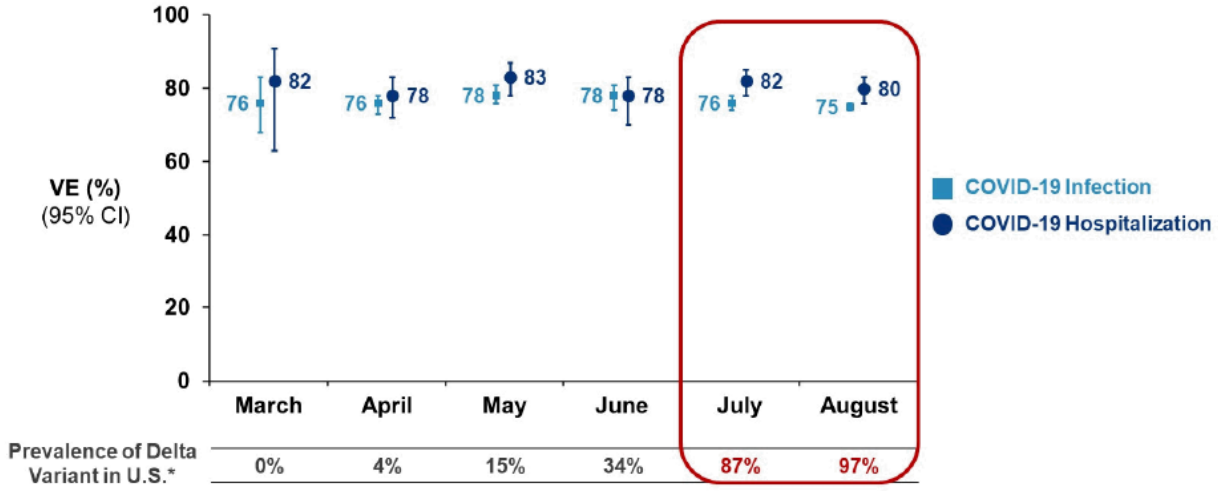
	Vaccinated Cases (N)[a] Person-yrs[b]	**Unvaccinated Cases (N) Person-yrs**	**Uncorrected VE% (95% CI)**	**Corrected[c] VE% (95% CI)**
National Cohort				
Any observed COVID-19	2,632 141,717	25,749 481,083	66% (64%, 67%)	76% (75%, 77%)
COVID-19 hospitalization	440 142,047	5,245 484,198	72% (69%, 74%)	81% (78%, 82%)
Age <65				
Any observed COVID-19	1,880 97,790	19,155 325,147	68% (66%, 69%)	78% (77%, 79%)
COVID-19 hospitalization	188 98,044	2,862 327,629	78% (75%, 81%)	85% (83%, 87%)
Age ≥65				
Any observed COVID-19	752 43,927	6,722 155,775	61% (58%, 63%)	72% (70%, 74%)
COVID-19 hospitalization	252 44,004	2,350 156,437	62% (57%, 67%)	74% (70%, 77%)
Immunocompromised				
Any observed COVID-19	246 9,915	1,753 34,969	51% (44%, 57%)	64% (59%, 68%)
COVID-19 hospitalization	68 9,946	519 35,183	54% (40%, 64%	67% (57%, 74%)
Non-Immunocompromised				
Any observed COVID-19	2,386 131,802	23,971 446,039	67% (65%, 68%)	77% (76%, 78%)
COVID-19 hospitalization	372 132,101	4,603 448,944	73% (70%, 75%)	83% (80%, 83%)

Source: Adapted from Appendix 5 of the Sponsor's Briefing Document
a. N=Total number of participants at risk per category
b. Person-years include time from vaccination (or matched index date for unvaccinated) to the documentation of any COVID-19 or COVID-19 hospitalization, or data cutoff
c. An assumed 40% under-ascertainment was used for all corrected VE estimates.

In general, the corrected VE estimates were 9-12% higher for all subgroups presented in Table 12. The uncorrected VE estimate for the national cohort was 66% (64%, 67%) for any observed COVID-19 and 72% (69%, 74%) for COVID-19-related hospitalization, with corrected VE estimates rising to 76% (75%, 77%) and 81% (78%, 82%) for the two endpoints, respectively. The VE estimate for those less than 65 years of age was higher both endpoints compared to VE for those 65 years of age and older. The VE estimates for immunocompromised individuals were lower than for non-immunocompromised individuals.

To explore the effectiveness of Ad26.COV2.S against variants of concern using real-world data, a month-over-month calculation of vaccine effectiveness was performed (Figure 3). Estimates for VE (which did not control for time since vaccination) were generally consistent month-over-month, with similar levels of effectiveness in June, July and August, during which Delta was the predominant strain circulating in the United States. Corrected VE estimates remain stable, between 75-78% for any observed COVID-19, and between 78-83% for COVID-19-related hospitalization.

Figure 3. Month-over-Month Corrected Vaccine Effectiveness for the National Cohort for COVID-19 Infection and Covid-19-related Hospitalization



4.3.3 Study COV4002 Summary and Limitations

The FDA summary of study COV4002 is based on the study report submitted by the Sponsor, and the Sponsor's analyses have not been verified by FDA. The Sponsor's analyses suggest that a single-dose (as documented by claims data in Health Verity) has an estimated VE between 66% (uncorrected) and 76% (corrected) for any observed COVID-19 in the national cohort used in this analysis. The VE for COVID-19-related hospitalization is estimated to be between 72% (uncorrected) and 81% (corrected) for the national cohort. These numbers are similar to the VE estimates from study COV3001, although there are a number of limitations and confounding factors to consider. The study analyses may incur substantial bias in VE estimates due to exposure misclassification, where vaccination may go undocumented due to the availability of vaccines at mass vaccination clinics, pharmacies, and other locations that may not link to the Health Verity dataset. To account for the under-ascertainment of vaccination in the unvaccinated cohort, it was proposed to conduct a sensitivity analysis that assumes a varying percentage of undocumented vaccinations in the unvaccinated cohort. Additionally, the proposed matching strategy would not fully account for differences in socioeconomic status and geography, as 3-digit zip codes are insufficient to capture local differences in individual

characteristics that are known to influence both COVID-19 outcomes and vaccination exposure (such as income, employment in service/other sectors, level of education, and race, for example). This may lead to multiple sources of confounding being included in the estimates of VE. Finally, the generalizability of this study cohort to all individuals receiving a single dose of Ad26.COV2.S may be limited, as it reflects only a small portion (396,517) of the total (~15 million) doses given in the United States, and may not be a random sample of the total Ad26.COV2.S vaccinated population.

4.4 Study Evaluating 6-Month Booster Dose (COV1001 Cohort 2a)

4.4.1 Study Design

Study COV1001 is an ongoing randomized, double-blind, placebo-controlled, Phase 1 study in healthy adult cohorts 18 through 55 years of age and ≥65 years of age to evaluate the safety and immunogenicity of two different dose levels of Ad26.COV2.S administered as a single dose or 2-dose schedule, at varying intervals. The study included 5 cohorts, with 5 groups within each cohort. Data for groups vaccinated with a single dose of $5x10^{10}$ vp or one or two doses of $1x10^{11}$ vp will not be discussed in this briefing document. The following table summarizes the study groups with available, relevant data on the immunogenicity after an additional dose of Ad26.COV2.S at $5x10^{10}$ vp after a first vaccination at the same dose level. Only Cohort 2a (6-month interval) is discussed in this section. Cohorts 1a and 3 (2- and 3-month intervals) will be discussed in further detail in Section 4.5.2.

Table 13. Relevant Groups from COV1001 With Available Data (All Doses: $5x10^{10}$ vp)

Cohort	Group	Interval Between Primary Vaccination and Second/Booster Dose	Immunogenicity data N	Age of participants (years)
2a	2	6 months	17	18-55
1a	1	2 months	25	18-55
3	1	3 months	25	≥65

4.4.2 Immunogenicity

In Cohort 2a, Group 2, 29 healthy adults between the ages of 18 and 55 were enrolled to receive a booster dose of Ad26.COV2.S at $5x10^{10}$ vp 6 months after primary vaccination with Ad26.COV2.S at the same dose level. Of the 29 participants who received one dose, only 19 participants went on to receive a booster dose at 6 months.

Humoral immune response to Ad26.COV2.S, measured by both neutralizing antibody titers and binding antibodies against SARS-CoV-2, was assessed as a secondary endpoint of the study. SARS-CoV-2 neutralizing titers were assessed using a psVNA performed by Janssen Bioassay Development and Automation. Responses were measured using pseudotyped particles harboring the spike protein from the reference strain (WA1/2020 with D614G mutation). Note that this psVNA assay is not yet qualified or validated and is different from the wtVNA assay used for the other study cohorts in COV1001.

Geometric mean titers (GMTs) of neutralizing antibodies as assessed by psVNA at various time points in participants in Cohort 2a who were primed with the $5x10^{10}$ vp Ad26.COV2.S and boosted with $5x10^{10}$ vp Ad26.COV2.S at 6 months post-primary regimen (Group 2) are shown in Table 14. As can be seen in the table, only 12% of participants mounted a measurable immune response at one month post-primary vaccination, which increased to 59% at 6 months post-

primary vaccination (pre-booster). After booster, 100% of study participants had a measurable immune response. The overall low immune response (below the level of detection) observed at Day 29 in this healthy, non-elderly adult study group is unexpected given the immunogenicity results observed at the same time point in other study cohorts within COV1001 when using a wild type neutralizing antibody assay. It is likely that the results seen are due to the low sensitivity of the psVNA assay used.

Table 14. SARS-CoV-2 Neutralization Per psVNA Against WA1/2020 with D614G Mutation (IC50; Janssen Bioassay Development and Automation), COV1001 Cohort 2a Group 2, Per Protocol Immunogenicity Set

	Baseline (D1)	28 Days Post-Primary Vaccination (D29)	Pre-Booster (D183)	7 Days Post-Booster (D190)	28 Days Post-Booster (D211)
N	17	17	17	17	15
Geometric mean (95% CI)	<LOD (NE, NE)	<LOD (<LOD, <LOD)	32 (<LOD, 67)	136 (89, 209)	209 (144, 303)
Positive sample n (%) (95% CI)	0 (0, 20)	2 (12%) (1, 36)	10 (59%) (33, 82)	17 (100%) (80, 100)	15 (100%) (78, 100)
Geometric mean increase (95% CI) from baseline	n/a	1.1 (0.9, 1.2)	2.1 (1.2, 3.9)	6.8 (4.4, 10.5)	10.5 (7.2, 15.1)
Geometric mean increase (95% CI) from booster	n/a	n/a	n/a	3.2 (2.3, 4.3)	4.5 (2.8, 7.3)

Source: Table 2, addendum-interim-tlr-vac31518cov1001.pdf
LOD: limit of detection (LOD=20)
Positive sample refers to a quantifiable response

4.4.3 Sponsor's Post-Hoc Analysis of Immune Response Post-Booster Dose vs. Post-Primary Vaccination

Study COV1001 was not designed to include pre-specified immunobridging hypothesis testing of the immunogenicity endpoints to support inference of effectiveness of a booster dose. A post-hoc analysis was provided in the EUA amendment submission to evaluate the ratio of geometric mean titers of psVNA against the reference strain (WA1/2020 strain with D614G mutation) at 7 days and 28 days post-booster compared to 28 days post-primary vaccination in participants in Cohort 2a who were primed with the $5x10^{10}$ vp Ad26.COV2.S and boosted with $5x10^{10}$ vp Ad26.COV2.S at 6 months (Table 15). Although this analysis showed that the GMT ratios are above the FDA-recommended non-inferiority criteria (lower bound of the 95% CI >0.67), this was a post-hoc analysis that included data from only 17 participants. Furthermore, interpretation of GMT ratios may be confounded by low sensitivity of the assay resulting in titers below the limit of detection post-primary vaccination. No analysis of difference in seroresponse rates (post-booster - post-primary vaccination) was provided.

Table 15. Post-Hoc Analysis: Ratio of GMTs at Day 29 Post-Primary Vaccination Versus 7 Days and 28 Days Post-Booster Dose Measured by psVNA Against WA1/2020 with D614G Mutation (IC50; Janssen Bioassay Development and Automation), Study COV1001 Cohort 2a Group 2, PPI Set

	Post-Booster N GMT (95% CI)	Post-Primary Vaccination (Day 29) N GMT (95% CI)	GMT Ratio (Booster/Primary)
7 Days Post Boost	N=17 136 (89, 209)	N=17 <LOD (<LOD, <LOD)	6.3 (4.4, 9.0)
28 Days Post Boost	N=15 209 (144, 303)	N=17 <LOD (<LOD, <LOD)	9.6 (7.0, 13.1)

Source: Table 3, addendum-interim-tlr-vac31518cov1001.pdf
LOD: limit of detection
For this analysis, values below LOD at D29 were imputed with LOD

A descriptive analysis of neutralizing antibody response against the SARS-CoV-2 Delta variant was conducted for the same 17 participants in Cohort 2a, Group 2 with pre- and post-booster dose samples. Only the time points of 6 months post-primary vaccination (pre-booster dose) and 7 and 28 days post-booster dose were assessed. As shown in Table 16, at 6 months post-primary vaccination, only 24% of participants had detectable neutralizing antibody titers against the Delta variant. After the booster dose was administered, detectable titers were observed in 100% of study participants, with a geometric mean increase of 2.2-fold and 3.0-fold increase from pre-boost at the 7 and 28 day time points, respectively. At all time points evaluated, the geometric mean titers against the Delta variant were lower than the titers observed against the reference strain (Table 14).

Table 16. Pseudovirus Neutralizing Antibody (IC50) GMTs Against Delta Variant (B.1.617.2), COV1001 Cohort 2a Group 2, PPI Set

	Pre-Booster (D183)	7 Days Post-Booster (D190)	28 Days Post-Booster (D211)
N	17	17	15
Geometric Mean (95% CI)	<LOD (<LOD, 35)	68 (43, 109)	98 (64, 148)
Positive Sample n (%) (95% CI)	4 (24%) (7, 50)	17 (100%) (80, 100)	15 (100%) (78, 100)
Titer ≥100 n (%) (95% CI)	2 (12%) (1, 36)	3 (18%) (4, 43)	6 (40%) (16, 68)
Geometric mean increase (95% CI) from Booster	n/a	2.2 (1.8, 2.8)	3.0 (2.1, 4.2)

Source: Table 6, addendum-interim-tlr-vac31518cov1001.pdf

4.4.4 Limitations of Immunogenicity Analyses

The psVNA assay used for the immunogenicity analysis for Cohort 2a is non-validated and non-qualified assay (assay status: developed) and different from the wtVNA used in the immunogenicity analyses for the other cohorts within COV1001 as well as the analyses for COV1002 and COV2001. Thus, the immune response after a booster administered at 6 months post-primary vaccination cannot be directly compared to the immune response after a booster at 2 or 3 months from the other studies. The psVNA does not appear to be a fit for purpose assay for use in immunobridging analysis comparing GMT post-boost to GMT post-primary dose as the post-primary response was <LOD and did not allow for a meaningful comparison.

4.4.5 Safety

Cohort 2a, Group 2

A total of 19 participants who received the $5x10^{10}$ vp Ad26.COV2.S primary regimen and the $5x10^{10}$ vp booster dose at 6 months post-primary vaccination contributed to the safety analysis.

Solicited adverse reactions

Table 17 and Table 18 show the frequencies of solicited local and systemic adverse reactions within 7 days of a primary vaccination with $5x10^{10}$ vp Ad26.COV2.S and within 7 days of a booster dose of $5x10^{10}$ vp Ad26.COV2.S when given 6 months after the primary vaccination. The group of participants in Cohort 2a who received placebo at 6 months after primary vaccination with $5x10^{10}$ vp Ad26.COV2.S serves as a comparator arm for safety.

Solicited local reactions

The most frequently reported solicited local reaction after a booster dose was injection site pain (78.9%). The overall rate and severity of injection site pain was similar post booster dose compared to post-primary vaccination. In the group primed with Ad26.COV2.S and boosted with Ad26.COV2.S, the median duration of injection site pain was 2 days (range 1-4 days) after primary vaccination and 3 days (range 1-7 days) after booster. Erythema and swelling were reported rarely after primary vaccination and not reported by any participants after a booster dose in this study.

Table 17. Frequency of Solicited Local Adverse Reactions by Severity, Within 7 Days After Primary Vaccination Compared to After Booster Dose Among Participants in Cohort 2a Group 2, Study COV1001, FAS (Analyses Not Verified by FDA)

	Post-Primary Vaccination	Post-Booster Dose
	N=29 n (%)	N=19 n (%)
Any solicited local AR	**24 (82.8)**	**15 (78.9)**
Grade 3 or higher solicited local AR	**0**	**0**
Injection site pain		
Any	23 (79.3)	15 (78.9)
Grade 1	18 (62.1)	12 (63.2)
Grade 2	5 (17.2)	3 (15.8)
Erythema		
Any	1 (3.4)	0
Grade 1	1 (3.4)	0
Grade 2	0	0
Swelling		
Any	1 (3.4)	0
Grade 1	1 (3.4)	0
Grade 2	0	0

Source: Table 59, interim-tlr-vac31518cov1001.pdf
Injection site pain: Grade 1: does not interfere with activity; Grade 2: requires modification in activity or use of medication
Erythema: Grade 1: 25-50mm; Grade 2: 51-100mm
Swelling: Grade 1: 25-50 mm, Grade 2: 51-100mm

Solicited systemic ARs

The most frequently reported solicited systemic ARs after a booster dose were headache (47.4%), fatigue (26.3%), myalgia (21.1%), and nausea (10.5%). Overall, these ARs appear to be lower in frequency and milder in severity after the booster dose compared to after primary

vaccination, but because of the small number of subjects evaluated, reliable conclusions cannot be drawn. The median duration of each AR after a booster dose was similar to that reported after primary vaccination. Fever was reported by 10.3% of participants in this group after primary vaccination but not reported by any participant after the booster dose. A lower percentage of participants reported use of antipyretic or pain medication after the booster dose compared to after primary vaccination.

Table 18. Frequency of Solicited Systemic Reactions, by Severity, Within 7 Days After Dose 1 Compared to After Booster Among Participants in Cohort 2a Group 2, Study COV1001 (Analyses Not Verified by FDA)

Event	Post-Primary Vaccination N=29 n (%)	Post-Booster Dose N=19 n (%)
Any solicited systemic AR	**23 (79.3)**	**11 (57.9)**
Grade 3 or higher solicited systemic AR	**1 (3.4)**	**0**
Fatigue		
Any	17 (58.6)	5 (26.3)
Grade 1	8 (27.6)	3 (15.8)
Grade 2	9 (31.0)	2 (10.5)
Grade 3	0	0
Headache		
Any	16 (55.2)	9 (47.4)
Grade 1	6 (20.7)	5 (26.3)
Grade 2	9 (31.0)	4 (21.1)
Grade 3	1 (3.4)	0
Myalgia		
Any	17 (58.6)	4 (21.1)
Grade 1	8 (27.6)	2 (10.5)
Grade 2	9 (31.0)	2 (10.5)
Grade 3	0	0
Nausea		
Any	8 (27.6)	2 (10.5)
Grade 1	6 (20.7)	2 (10.5)
Grade 2	2 (6.9)	0
Grade 3	0	0
Fever		
Any	3 (10.3)	0
Grade 1	1 (3.4)	0
Grade 2	2 (6.9)	0
Grade 3	0	0
Antipyretic or pain medication use	12 (41.4)	6 (31.6)

Source: Table 61, interim-tlr-vac31518cov1001.pdf
Fatigue, Headache, Myalgia, Nausea – Grade 1: no interference with activities; Grade 2: requires modification in activity or use of medications; Grade 3: incapacitating; prevents daily activity; use of Rx pain reliever.
Fever – Grade 1: 38-38.4 C, Grade 2: 38.5-38.9 C

Unsolicited AEs

An overview of unsolicited adverse events within 28 days after each dose is presented in Table 19. As of the data cutoff date of July 21, 2021, there were no SAEs or AEs leading to discontinuation in Cohort 2a, Group 2.

Table 19. Overview of Unsolicited Adverse Events Within 28 Days After Primary Vaccination and After Booster Dose in Studies COV1001 Cohort 2a, Full Analysis Set (Analyses Not Verified by FDA)

	Ad26.COV2.S + Ad26.COV2.S Post-Primary Vaccination N=29 n[a] (%)	Ad26.COV2.S + Placebo Post-Primary Vaccination N=90 n[a] (%)	Ad26.COV2.S + Ad26.COV2.S Post -Booster Dose N=19 n[a] (%)	Ad26.COV2.S + Placebo Post-Booster Dose N=62 n[a] (%)
Unsolicited AE	5 (17.2)	22 (24.4)	2 (10.5)	2 (3.2)
Unsolicited AE of grade 3 or higher	0	0	0	0
Unsolicited AE considered related to study vaccine	2 (6.9)	10 (11.1)	1 (5.3)	0
Unsolicited grade 3 AE considered related to study vaccine	0	0	0	0
Serious Adverse Events	0	0	0	0
Deaths	0	0	0	0
AE leading to study discontinuation	0	0	0	0

Source: Table 57, interim-tlr-vac31518cov1001.pdf

4.4.6 Summary for COV1001

Based on a limited number of subjects from COV1001 Cohort 2a Group 2, a booster dose of Ad26.COV2.S given at 6 months after the primary vaccination elicited an increase in neutralizing antibody titers against the reference strain of at least 4-fold compared to pre-boost titers. A similar increase in immune response is seen when assessing for neutralizing antibody titers specifically against the Delta variant. These analyses were post hoc and relied upon non-qualified/non-validated assays. In this small study group, there were no concerning signal safety signals observed after a second dose, but no reliable conclusions can be drawn. The only data from COV1001 which has been independently verified by the FDA are the immunogenicity results from Cohort 2a, Group 2 (Tables 14, 15, 16).

4.5 Studies Evaluating 2 Doses (2- or 3-Month Intervals)

4.5.1 Study COV3009

4.5.1.1 Design

Study COV3009 is an ongoing Phase 3 randomized, multicenter, double-blind, placebo-controlled clinical trial originally designed to assess the efficacy and safety of 2 doses of $5x10^{10}$ vp Ad26.COV2.S given approximately 2-months apart (56-days +/- 14 days) for the prevention of COVID-19. Approximately 30,000 healthy adults 18 years of age and older were enrolled and randomized 1:1 to receive either two doses of $5x10^{10}$ vp Ad26.COV2.S or placebo. At least 30% of the total study population was to consist of participants ≥60 years of age, with enrollment of participants ages 18 to 40 years of age limited to approximately 20%.

Following the EUA authorization of Ad26.COV2.S by the U.S. FDA on Feb 27, 2021, a protocol amendment was introduced to individually unblind each participant and offer Ad26.COV2.S to those participants who originally received placebo. The protocol was continued with unblinded participants entering the open-label phase. Crossover vaccination with one single Ad26.COV2.S dose was offered to study participants in the placebo group, whereas newly enrolled participants were randomized to receive 1 or 2 doses of Ad26.COV2.S. These subjects were enrolled in the

open-label phase of the study and not included in the analysis of the double-blind phase, which is the focus of this overview.

COV3009 was conducted in multiple regions (North and South America, Africa, Europe, Asia) at a time when new variants of SARS-CoV-2 were emerging. Overall, the relative contribution of participants was 39% from the U.S., 41% from Europe (Belgium, France, Germany, Spain, and UK), 6.6% from South Africa, 8.5% from South America (Brazil, Columbia), and 5% from Asia (Philippines). At the time of this review, sequence data was available from roughly 68% of COVID-19 cases.

In general, the demographics were balanced between the vaccine arm and the placebo arm with 47% female participants and 53% male participants. Racial demographics included 76% white, 8.2% Black/African American, 8.7% Asian and 2.5% American Indian/Alaskan Native. The most common risk factors for severe COVID-19 disease included obesity (~25%), diabetes (~5.5%), and hypertension (~9%), which were present in 41% of participants and 1.2% of participants were positive for HIV at the time of enrollment.

Overall, 54% of participants enrolled received 2 doses of Ad26.COV2.S prior to unblinding. The median duration of blinded follow-up after the second dose was 36 days (range 0-172 days), with 29% of the participants having at least 2 months of blinded follow-up.

All participants were actively and passively monitored for acute, molecularly confirmed, symptomatic COVID-19, regardless of severity. Molecularly confirmed COVID-19 was determined using FDA-authorized PCR tests, confirmed at a central laboratory (University of Washington). The COVID-19 case definitions used in this study are described in the EUA review memorandum for the Janssen COVID-19 Vaccine.[6]

The primary objective of the study was to demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed moderate to severe/critical COVID-19, relative to placebo, in SARS-CoV-2 seronegative adults. The primary endpoint of the study was the first occurrence of molecularly confirmed moderate to severe/critical COVID-19, with onset at least 14 days after the second vaccination (Day 71). Secondary analyses evaluated the occurrence of molecularly confirmed severe/critical COVID-19, with onset 14 days after the second vaccination. The primary and secondary analyses were based on the per protocol efficacy set, defined in Section 4.1.

The summaries of efficacy data presented here reflect FDA's preliminary assessment based on the COV3009 study report; these efficacy analyses have not been independently verified from the datasets.

4.5.1.2 Vaccine Efficacy

Primary Analysis

The primary efficacy analysis (data cutoff June 25, 2021) included 16,751 (54%) subjects that were randomized 1:1 to receive 2 doses of Ad26.COV.2.S or placebo with a two-month interval. In total 8,653 subjects received 2 doses of Ad26.COV2.S in the double-blind phase, of which 8,594 subjects (99.3%) received a second dose within the protocol specific window and have been included in the per-protocol efficacy analysis set (second dose within 37 to 75 days since the first vaccination).

Vaccine efficacy (VE) at least 14 days following the second vaccination dose against central laboratory-confirmed moderate to severe/critical COVID-19 (primary efficacy endpoint) across all geographic areas in which the trial was conducted was 75.2% (adjusted 95% CI 54.55; 87.30). Study COV3009 also had predefined per protocol analyses of efficacy following a single dose of Ad26.COV2.S. Results of these analyses will not be discussed because the topline study results submitted by the Sponsor did not include sufficient information to understand how they were performed.

Subgroup analysis of the primary endpoint in age cohorts 18-59 and ≥60 years of age yielded efficacy point estimates of 77.6% (95% CI 54.44; 89.97) and 66.2% (95% CI -13.97; 92.16), respectively (Table 20).

Table 20. Vaccine Efficacy Against Centrally Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 Days After Dose 2 (Day ≥71), Primary Analysis, Study 3009, Per-Protocol Set (Analyses Not Verified by FDA)

Primary Endpoint Subgroup	Ad26.COV2.S Cases (N)[a] Person-yrs[b]	Placebo Cases (N) Person-yrs	VE% (95% CI)
All participants	14 (6024) 1729.99	52 (5615) 1594.98	75.2% (54.55; 87.30)
Age 18-59 years	10 (4692) 1386.93	41 (4359) 1276.36	77.6% (54.44; 89.97)
Age ≥60 years	4 (1332) 343.06	11 (1256) 318.61	66.2% (**-13.97**; 92.16)

Source: GEFPE02AS1, prelim-tlr-vac31518cov3009-p1.pdf
[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.

Additional subgroup analyses by country estimated VE against moderate to severe/critical COVID-19 as of 14 days after the second dose among U.S. participants at 93.7% (95% 58.45; 99.85). However, the confidence intervals for the U.S. estimate and those of other countries are overlapping, and the number of cases was small (with wide confidence intervals crossing zero) in some of the country subgroups.

Analyses of secondary endpoints demonstrated vaccine efficacy against central laboratory confirmed and blind-adjudicated severe/critical COVID-19 occurring at least 14 days following the second vaccination of 100% (adjusted 95% CI 32.62; 100.00), based on only 8 endpoint cases (Table 21). Analyses of COVID-19 cases requiring medical intervention and COVID-19 related deaths included even fewer cases, precluding calculation of confidence intervals.

Table 21. Secondary Endpoints of Vaccine Efficacy Against Centrally Confirmed COVID-19 With Onset at Least 14 Days After Dose 2 (Day ≥71), Study 3009, Per-Protocol Set (Analyses Not Verified by FDA)

Primary Endpoint Subgroup	Ad26.COV2.S N[a]=6024 Cases Person-yrs	Placebo N[a]=5615 Cases Person-yrs	VE% (95% CI)
Severe/critical COVID-19	0 1730.72	8 1598.87	100.0% (32.62; 100.00)
COVID-19 requiring medical intervention	0 1730.72	5 1599.05	Not Calculated

Primary Endpoint Subgroup	Ad26.COV2.S N[a]=6024 Cases Person-yrs	Placebo N[a]=5615 Cases Person-yrs	VE% (95% CI)
COVID-19 related deaths	0 1730.72	1 1599.41	Not Calculated

Source: TEFSUM01A, prelim-tlr-vac31518cov3009-p1.pdf
a N=Total number of participants at risk per category

Vaccine Efficacy Against Variants

Sequence data was available for approximately 68% of COVID-19 cases from the full analysis set at the time of the primary analysis (Table 22). Of the sequenced cases, the most prevalent variants were B.1.1.7 (Alpha) at 38.2%, B.1.621 (Mu) at 14.1%, B.1.351 (Beta) at 7.2%, B.1.617.2/AY.1/AY.2 (Delta) at 4.1%, and P.1 (Gamma) at 4.1% (Table 22).

Table 22. Proportion of Molecularly Confirmed Cases Infected With SARS-CoV-2 Variant With S Protein Amino Acid Variation Versus the SARS-CoV-2 Reference Sequence With Substitution Profile for Blinded Subjects, Study 3009, Full Analysis Set (Numbers Not Verified by FDA)

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

Source: TVICE COV02 B1, prelim-tlr-vac31518cov3009-p1.pdf

Secondary analyses of VE at least 14 days following the second vaccination dose against central laboratory-confirmed moderate to severe/critical COVID-19 by virus variant was performed. However, case numbers in the per protocol set were small, resulting in wide confidence intervals. Secondary analyses of VE at least 14 days following dose 2 for the Delta variant included 2 cases in the vaccinated group and 1 case in the placebo group, precluding the calculation of estimated VE for this variant. Sufficient numbers were available to perform a calculation of the estimated VE for variants B.1.1.7 (Alpha) and B.1.621 (Mu), with an estimated VE of 94.2% (95% CI 62.91; 99.86) and 63.1% (95% CI -27.86; 91.56), respectively.

4.5.1.3 Safety

The primary safety objective in study COV3009 was to describe the safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months after the last double-blind vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants. A safety subset of approximately 6000 participants was used to evaluate safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after each vaccination, and in terms of unsolicited AEs during 28 days after each vaccination (Table 23). The summaries of safety data presented here reflect FDA's preliminary assessment based on the COV3009 study report; these safety analyses have not been independently verified from the datasets.

Table 23. Disposition, Safety Analysis Population, Study 3009 (Numbers Not Verified by FDA)

Disposition	Ad26.COV2.S n (%)	Placebo n (%)	Total n (%)
Randomized	15976	15859	31835
Vaccinated[a]	15708	15592	31300
Vaccinated with incorrect vaccine	55	5	60
Full analysis set	15708 (100.0%)	15592 (100.0%)	31300 (100.0%)
Participants with ≥8 weeks follow-up	11412 (72.7%)	10872 (69.7%)	22284 (71.2%)
Participants unblinded to treatment	15472 (98.5%)	15298 (98.1%)	30769 (98.3%)
Discontinued from study	701 (4.5%)	1758 (11.3%)	2459 (7.9%)
Reason for discontinuation			
Withdrawal by participant	468 (3.0%	1273 (8.2%)	1741 (5.6%)
Death	6 (<0.1%	13 (0.1%)	19 (0.1%)
Lost to follow-up	170 (1.1%	219 (1.4%)	389 (1.2%)
Physician decision	15 (0.1%	6 (<0.1%)	21 (0.1%)
Protocol deviation	1 (<0.1%	7 (<0.1%)	8 (<0.1%)
Other	41 (0.3%	240 (1.5%)	281 (0.9%)
Safety subset N (% of full analysis set) post dose 1	3016 (19.2%)	3052 (19.6%)	6068 (19.4%)
Completed post-vaccination period (Day 1-29)[b] post dose 1	2869 (95.1%)	2853 (93.5%)	5722 (94.3%)
Safety subset N (% of full analysis set) post dose 2	1559 (9.9%)	1425 (9.1%)	2984 (9.5%)
Completed post-vaccination period (Day 1-29)[b] post dose 2	1032 (66.1%)	942 (66.1%)	1974 (66.1%)

a These values are denominators for the percentage calculations
b Percentage based on Safety subset
Source: Compiled from table(s) provided by Sponsor

Table 24. Participants Reporting at Least One Adverse Event, Among All Participants and by Age Group, Study COV3009 Double-Blind Phase, Full Analysis Set (Analyses Not Verified by FDA)

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Full analysis set	N=15705	N=15588
18-59 years of age	N=10087	N=9975
≥60 years of age	N=5617	N=5613
Medically attended adverse event		
18-59 years of age	669 (6.6%)	640 (6.4%)
≥60 years of age	364 (6.5%)	363 (6.5%)
Related medically attended adverse events		
18-59 years of age	62 (0.6%)	34 (0.3%)
≥60 years of age	30 (0.5%)	16 (0.3%)

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Serious adverse event		
18-59 years of age	55 (0.5%)	65 (0.7%)
≥60 years of age	49 (0.9%)	71 (1.3%)
Related serious adverse event		
18-59 years of age	4 (<0.1%)	2 (<0.1%)
≥60 years of age	4 (0.1%)	1 (<0.1%)
Deaths		
18-59 years	2 (<0.1%)	8 (0.1%)
≥60 years	2 (<0.1%)	5 (0.1%)
Related deaths	0	1 (<0.1%)
AEs leading to study discontinuation	5 (<0.1%)	9 (0.1%)

Sources: Compiled from table(s) provided by Sponsor

Table 25. Participants Reporting at Least One Adverse Event, Among All Participants and by Age Group, Study COV3009 Double-Blind Phase, Safety Set (Analyses Not Verified by FDA)

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Safety subset	N=3016	N=3052
Post-Dose 1		
18-59 years of age	**N=1784**	**N=1822**
≥60 years of age	**N=1231**	**N=1230**
Solicited local adverse reaction		
18-59 years of age	1170 (65.6%)	445 (24.4%)
≥60 years of age	506 (41.1%)	208 (16.9%)
Grade 3 solicited local adverse reaction[a]		
18-59 years of age	7 (0.4%)	4 (0.2%)
≥60 years of age	2 (0.2%)	2 (0.2%)
Solicited systemic adverse reaction		
18-59 years of age	1194 (66.9%)	767 (42.1%)
≥60 years of age	570 (46.3%)	371 (30.2%)
Grade 3 solicited systemic adverse reaction[a]		
18-59 years of age	44 (2.5%)	8 (0.4%)
≥60 years of age	11 (0.9%)	6 (0.5%)
Unsolicited adverse event up to 28 days after vaccination		
18-59 years of age	272 (15.2%)	226 (12.4%)
≥60 years of age	182 (14.8%)	106 (8.6%)
Grade 3 unsolicited adverse event		
18-59 years of age	10 (0.6%)	9 (0.5%)
≥60 years of age	8 (0.6%)	5 (0.4%)
Grade 4 unsolicited adverse event		
18-59 years of age	2 (0.1%)	0
≥60 years of age	1 (0.1%)	2 (0.2%)
Related[b] unsolicited adverse events		
18-59 years of age	175 (9.8%)	130 (7.1%)
≥60 years of age	108 (8.8%)	49 (4.0%)
Post-Dose 2		
18-59 years of age	**N=1164**	**N=1077**
≥60 years of age	**N=395**	**N=348**
Solicited local adverse reaction		
18-59 years of age	726 (62.4%)	209 (19.4%)
≥60 years of age	170 (43.0%)	43 (12.4%)

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Grade 3 solicited local adverse reaction[a]		
18-59 years of age	7 (0.6%)	2 (0.2%)
≥60 years of age	3 (0.8%)	1 (0.3%)
Solicited systemic adverse reaction		
18-59 years of age	657 (56.4%)	353 (32.8%)
≥60 years of age	164 (41.5%)	89 (25.6%)
Grade 3 solicited systemic adverse reaction[a]		
18-59 years of age	21 (1.8%)	3 (0.3%)
≥60 years of age	4 (1.0%)	2 (0.6%)
Unsolicited adverse event up to 28 days after vaccination		
18-59 years of age	124 (10.7%)	93 (8.6%)
≥60 years of age	35 (8.9%)	27 (7.8%)
Grade 3 unsolicited adverse event		
18-59 years of age	7 (0.6%)	6 (0.6%)
≥60 years of age	5 (1.3%)	1 (0.3%)
Grade 4 unsolicited adverse event		
18-59 years of age	0	0
≥60 years of age	0	0
Related[b] unsolicited adverse events		
18-59 years of age	62 (5.3%)	39 (3.6%)
≥60 years of age	17 (4.3%)	10 (2.9%)

Sources: Compiled from table(s) provided by Sponsor

Solicited adverse events

Overall, the frequency of solicited local adverse events was similar post dose 1 versus post dose 2 (Table 26). The median time of onset and median duration of solicited local adverse events was also similar post dose 1 vs post dose 2 (Table 27). There was a trend toward a decreased frequency of longer duration (>7 days) symptoms post dose 2 relative to post dose 1 (Table 27).

Overall, there was a trend toward decreased frequencies of solicited systemic adverse events following dose 1 relative to dose 2 (Table 28). Similar to the solicited local events described above, there were similar median times of onset and median duration of symptoms post dose 1 versus post dose 2. There was likewise a similar trend toward decreased frequency of longer duration (>7 days) symptoms post dose 2 relative to post dose 1 (Table 29).

Table 26. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Vaccination, Safety Subset, Study 3009 (Analyses Not Verified by FDA)

Adverse Reaction	Dose 1 18-59 Years Ad26.COV2.S N=1784 n (%)	Dose 2 18-59 years Ad26.COV2.S N=1164 n (%)	Dose 1 ≥60 Years Ad26.COV2.S N=1231 n (%)	Dose 2 ≥60 Years Ad26.COV2.S N=395 n (%)
Any Local	1170 (65.6%)	726 (62.4%)	506 (41.1%)	170 (43.0%)
Grade 3	7 (0.4%)	7 (0.6%).	2 (0.2%)	3 (0.8%)
Pain	1141 (64.0%)	715 (61.4%)	493 (40.0%)	162 (41.0%)
Grade 3	3 (0.2%)	2 (0.2%)	0	1 (0.3%)
Erythema	204 (11.4%)	113 (9.7%)	59 (4.8%)	15 (3.8%)
Grade 3	2 (0.1%)	5 (0.4%)	0	2 (0.5%)

Adverse Reaction	Dose 1 18-59 Years Ad26.COV2.S N=1784 n (%)	Dose 2 18-59 years Ad26.COV2.S N=1164 n (%)	Dose 1 ≥60 Years Ad26.COV2.S N=1231 n (%)	Dose 2 ≥60 Years Ad26.COV2.S N=395 n (%)
Swelling	130 (7.3%)	81 (7.0%)	37 (3.0%)	7 (1.8%)
Grade 3	2 (0.1%)	2 (0.2%)	2 (0.2%)	2 (0.5%)

Sources: Compiled from table(s) provided by Sponsor
Pain- Grade 3: any use of Rx pain reliever/prevents daily activity;
Erythema and swelling/induration- Grade 3: >100mm;

Table 27. Time (Days) to Onset and Duration of Solicited Local Adverse Events, Safety Subset, Study 3009 (Analyses Not Verified by FDA)

Adverse Reaction	Dose 1 Ad26.COV2.S N=3015	Dose 2 Ad26.COV2.S N=1559
Pain, n (%)	1634 (54.2%)	877 (56.3%)
Median time to onset (min, max)	2.0 (1; 8)	1.0 (1; 8)
Median duration (min, max)	3.0 (1; 29)	2.0 (1; 18)
>7 days duration	62 (3.7%)	16 (1.8%)
Erythema, n (%)	263 (8.7%)	128 (8.2%)
Median time to onset (min, max)	2.0 (1; 8)	2.0 (1; 5)
Median duration (min, max)	3.0 (1; 33)	3.0 (1; 25)
>7 days duration	22 (1.3%)	5 (0.6%)
Swelling, n (%)	167 (5.5%)	88 (5.6%)
Median time to onset (min, max)	2.0 (1; 8)	2.0 (1; 8)
Median duration (min, max)	2.0 (1; 23)	2.0 (1; 16)
>7 days duration	8 (0.5%)	2 (0.2%)

Source: Compiled from table(s) provided by Sponsor

Table 28. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Vaccination, Safety Subset, Study 3009 (Analyses Not Verified by FDA)

Adverse Reaction	Dose 1 18-59 Years Ad26.COV2.S N=1784 n (%)	Dose 2 18-59 years Ad26.COV2.S N=1164 n (%)	Dose 1 ≥60 Years Ad26.COV2.S N=1231 n (%)	Dose 2 ≥60 Years Ad26.COV2.S N=395 n (%)
Any Systemic	1194 (66.9%)	657 (56.4%)	570 (46.3%)	164 (41.5%)
Grade 3	44 (2.5%)	21 (1.8%)	11 (0.9%)	4 (1.0%)
Fatigue	951 (53.3%)	528 (45.4%)	404 (32.8%)	113 (28.6%)
Grade 3	22 (1.2%)	11 (0.9%)	4 (0.3%)	3 (0.8%)
Headache	901 (50.5%)	444 (38.1%)	390 (31.7%)	114 (28.9%)
Grade 3	18 (1.0%)	8 (0.7%)	5 (0.4%)	2 (0.5%)
Myalgia	841 (47.1%)	438 (37.6%)	331 (26.9%)	103 (26.1%)
Grade 3	20 (1.1%)	7 (0.6%)	3 (0.2%)	2 (0.5%)
Nausea	375 (21.0%)	176 (15.1%)	171 (13.9%)	49 (12.4%)
Grade 3	8 (0.4%)	1 (0.1%)	1 (0.1%)	2 (0.5%)

Adverse Reaction	Dose 1 18-59 Years Ad26.COV2.S N=1784 n (%)	Dose 2 18-59 years Ad26.COV2.S N=1164 n (%)	Dose 1 ≥60 Years Ad26.COV2.S N=1231 n (%)	Dose 2 ≥60 Years Ad26.COV2.S N=395 n (%)
Fever	122 (6.8%)	29 (2.5%)	28 (2.3%)	9 (2.3%)
Grade 3	2 (0.1%)	1 (0.1%)	0	0
Antipyretic/ Analgesic Use*	384 (21.5%)	207 (17.8%)	118 (9.6%)	36 (9.1%)

Source: Compiled from table(s) provided by Sponsor
* Number of Subjects With use of Antipyretics/Analgesics Within 7 Days Post Vaccination (Source: ICM11).
Fatigue, Headache, Myalgia – Grade 3: incapacitating; prevents daily activity; use of Rx pain reliever. Grade 4: Requires E.R. visit or hospitalization
Nausea –Grade 3: incapacitating; prevents daily activity. Grade 4: Requires E.R. visit or hospitalization
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

Table 29. Time (Days) to Onset and Duration of Solicited Adverse Events, Safety Subset, Study 3009 (Analyses Not Verified by FDA)

Adverse Reaction	Dose 1 Ad26.COV2.S N=3015	Dose 2 Ad26.COV2.S N=1559
Fatigue, n (%)	1355 (44.9%)	641 (41.1%)
Median time to onset (min, max)	2.0 (1; 8)	2.0 (1; 8)
Median duration (min, max)	2.0 (1; 56)	2.0 (1; 29)
>7 days duration	52 (2.9%)	18 (2.2%)
Headache, n (%)	1291 (42.8%)	558 (35.8%)
Median time to onset (min, max)	2.0 (1; 8)	2.0 (1; 8)
Median duration (min, max)	1.0 (1; 40)	1.0 (1; 15)
>7 days duration	35 (2.0%)	13 (1.6%)
Myalgia, n (%)	1172 (38.9%)	541 (34.7%)
Median time to onset (min, max)	2.0 (1; 8)	2.0 (1; 8)
Median duration (min, max)	2.0 (1; 28)	1.0 (1; 13)
>7 days duration	37 (2.1%)	15 (1.8%)
Nausea, n (%)	546 (18.1%)	225 (14.4%)
Median time to onset (min, max)	2.0 (1; 8)	2.0 (1; 8)
Median duration (min, max)	1.0 (1; 28)	1.0 (1; 13)
>7 days duration	11 (0.6%)	5 (0.6%)
Fever, n (%)	150 (5.0%)	38 (2.4%)
Median time to onset (min, max)	2.0 (1; 6)	2.0 (1; 7)
Median duration (min, max)	1.0 (1; 16)	1.0 (1; 8)
>7 days duration	3 (0.2%)	2 (0.2%)

Source: Compiled from table(s) provided by Sponsor

Unsolicited adverse events

Table 30 and Table 31 present the unsolicited adverse events occurring in ≥1% of participants within 28 days following dose 1 and dose 2 according to MedDRA primary System Organ Class and Preferred Terms. The most common unsolicited adverse events post dose 1 were fatigue (n=105, 3.5%) and headache (n=107, 3.5%), similar to the placebo group (fatigue n=94, 3.1%, headache n=98, 3.2%). The most common unsolicited adverse events post dose 2 were also fatigue (n=29, 1.9%) and headache (n=34, 2.2%), likewise similar to the placebo group (fatigue n=28, 2.0%, headache n=25, 1.8%). No severe unsolicited adverse events were reported.

Table 30. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants Within 28 Days Following Dose 1, Safety Subset, Study 3009 (Analyses Not Verified by FDA)

System Organ Class Preferred Term	Ad26.COV2.S N=3015 Any Grade n (%)	Ad26.COV2.S N=3015 ≥Grade 3 n (%)	Placebo N=3052 Any Grade n (%)	Placebo N=3052 ≥Grade 3 n (%)
General disorders and administration site conditions	241 (8.0%)	3 (0.1%)	136 (4.5%)	3 (0.1%)
Fatigue	105 (3.5%)	2 (0.1%)	94 (3.1%)	2 (0.1%)
Vaccination site pain	66 (2.2%)	0	19 (0.6%)	0
Nervous system disorders	121 (4.0%)	8 (0.3%)	108 (3.5%)	3 (0.1%)
Headache	107 (3.5%)	8 (0.3%)	98 (3.2%)	3 (0.1%)
Musculoskeletal and connective tissue disorders	120 (4.0%)	5 (0.2%)	85 (2.8%)	2 (0.1%)
Myalgia	82 (2.7%)	2 (0.1%)	66 (2.2%)	1 (<0.1%)
Gastrointestinal disorders	60 (2.0%)	3 (0.1%)	47 (1.5%)	3 (0.1%)
Nausea	33 (1.1%)	2 (0.1%)	29 (1.0%)	2 (0.1%)

Source: Compiled from table(s) provided by Sponsor
N=Number of subjects at risk post-dose 1
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The same event in one subject in the post-dose 1 period and in the post-dose 2 period will be counted once in the post-dose 1 and post-dose 2 Combined period.
Notes: Adverse events are coded using MedDRA Version 24.0.This table displays the grade 3 events from the set of events that occur >=1% in the Ad26 5e10 Group.

Table 31. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants Within 28 Days Following Dose 2, Safety Subset, Study 3009 (Analyses Not Verified by FDA)

System Organ Class Preferred Term	Ad26.COV2.S N=1559 Any Grade n (%)	Ad26.COV2.S N=1559 ≥Grade 3 n (%)	Placebo N=1425 Any Grade n (%)	Placebo N=1425 ≥Grade 3 n (%)
General disorders and administration site conditions	63 (4.0%)	2 (0.1%)	43 (3.0%)	1 (0.1%)
Fatigue	29 (1.9%)	1 (0.1%)	28 (2.0%)	1 (0.1%)
Nervous system disorders	38 (2.4%)	2 (0.1%)	28 (2.0%)	0
Headache	34 (2.2%)	1 (0.1%)	25 (1.8%)	0
Musculoskeletal and connective tissue disorders	35 (2.2%)	1 (0.1%)	33 (2.3%)	3 (0.2%)
Myalgia	22 (1.4%)	1 (0.1%)	22 (1.5%)	0

Source: Compiled from table(s) provided by Sponsor
N=Number of subjects at risk post-dose 2
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The same event in one subject in the post-dose 1 period and in the post-dose 2 period will be counted once in the post-dose 1 and post-dose 2 Combined period.
Notes: Adverse events are coded using MedDRA Version 24.0.This table displays the grade 3 events from the set of events that occur >=1% in the Ad26 5e10 Group.

Adverse events of special interest

Overall, for the entire double-blind phase of the study (Ad26.COV2.S N=15705, placebo N= 15588) the number of subjects with at least one recorded adverse event of special interest (AESI) reported by the investigator was 13 (0.1%) in the vaccinated group and 21 (0.1%) in the placebo group. Among all AESIs, 11 of the 13 (84.6%) events from the vaccinated group and 16 of the 21 (76.2%) events from the placebo group were retrieved using the SMQ ”Embolic and thrombotic events,” and 2 of the 13 (15.4%) events from the vaccinated group and 5 of the 21 (23.8%) events from the placebo group were retrieved using the SMQ “Thrombocytopenia.”

Post-dose 1 there were 2 (<0.1%) reported AESIs in the vaccinated group and 6 (<0.1%) reported adverse events of special interest in the placebo group. All of these AESI were retrieved using the SMQ ”Embolic and thrombotic events.” There was 1 arterial embolic event reported in the vaccinated group and 4 reported in the placebo group. There were 0 venous thromboembolic events reported in the vaccinated group; however, there were 2 reported in the placebo group. There was 1 uncharacterized embolic event recorded in the vaccinated group that was not reported in the placebo group.

Post-dose 2 there were 2 (<0.1%) reported AESI in both the vaccinated group and the placebo group. All of these AESI were retrieved using the SMQ ”Embolic and thrombotic events.” There was 1 reported pulmonary embolism and 1 reported cerebrovascular accident in the vaccinated group and 2 reported myocardial infarctions in the placebo group.

Serious adverse events (SAEs)

During blinded follow-up, among 15705 vaccine recipients and 15588 placebo recipients followed for a median of 70 days post-dose 1 and 4 days post-dose 2, a total of 104 participants reported one or more SAEs in the vaccinated group (18-59 years of age n=55, 0.5%; ≥60 n=49, 0.9%) and 136 participants reported one or more SAEs in the placebo group (18-59 years of age n=65, 0.7%; ≥60 n=71, 1.3%). During blinded follow up, 8 participants reported SAEs considered by the Sponsor or investigator as related to study vaccine in the vaccinated group (0.1%), compared to 3 (<0.1%) in the placebo group. Narratives of SAEs were not submitted by the Sponsor (which limits FDA’s assessment of causal relationship), but the following information about SAEs considered related by the Sponsor or investigator, and all fatal SAEs, was constructed from the datasets.

During the blinded follow-up phase, a total of five participants reported SAEs assessed as related by the investigator after dose 1 of Ad26.COV2.S. A participant in the 18-59 years of age cohort with a history of obesity reported an SAE of injection site swelling Day 2 after dose 1, and on Day 10 after dose 1, the participant had vertigo and myocardial necrosis marker increased, which required hospitalization for a duration of 4 days. The outcome of all events was recovered/resolved. Two additional participants reported events within 2 days following vaccination, including an SAE of pyrexia on Day 1 in a participant in the ≥60 years of age cohort, which was considered an important medical event, and an SAE of allergy to vaccine on Day 2 in a participant in the 18-59 years of age cohort, which was considered life-threatening and required treatment with epinephrine and steroids. Both events were considered recovered/resolved. One participant in the ≥60 years of age cohort reported an SAE of pericarditis requiring hospitalization on Day 11 after dose 1. She was hospitalized for 21 days. An imputed duration of the event was 111 days, with an outcome of recovering/resolving. One participant in the ≥60 years of age cohort with a relevant history of hypertension and cerebrovascular accident reported an SAE of hemoptysis on Day 67 after dose 1, which was considered a medically important event, with a duration of 2 days and an outcome of recovered/resolved.

A total of three participants reported SAEs assessed as related by the investigator after dose 2 of Ad26.COV2.S in the blinded follow-up phase, including a participant in the 18-59 years of age cohort with an SAE of facial paresis Day 67 after dose 1 and Day 11 after dose 2 which was considered a medically important event, with a duration of 25 days and an outcome of recovered/resolved. A participant in the 18-59 years of age cohort with no reported medical history reported an SAE of cerebrovascular accident on Day 134 after dose 1 and Day 79 after dose 2. This event was considered life-threatening, and he was seen in the emergency department on study Days 134 and 135 and treated with enoxaparin on Day 135. The duration

of the event was 1 day, and the outcome was considered recovered/resolved. A participant in the ≥60 years of age cohort reported an SAE of pulmonary embolism on Day 60 after dose 1 and Day 10 after dose 2 which was considered life-threatening, required hospitalization and had an outcome of not recovered/not resolved. However, this participant was unblinded on the day of onset of the SAE, and it is unclear whether the causality assessment preceded unblinding.

Additionally, total of four participants reported SAEs considered related to Ad26.COV2.S after unblinding (open-label phase), all of which were thrombotic events or potential thrombotic events (cerebrovascular accident). Two participants reported these events within 31 days of dose 2, including events of thrombosis (age ≥ 60 years) Day 21 after dose 2, and cerebrovascular accident Day 31 after dose 2, both of which required hospitalization with an outcome of recovered/resolved. Two participants reported SAEs of venous thrombosis that were more temporally distant from the most recent vaccine dose, including an event of venous thrombosis limb in a participant in the 18-59 years of age cohort Day 58 after dose 2, and an event of deep venous thrombosis reported on Day 100 after dose 1 in a participant in the ≥60 years of age cohort who also reported related SAEs of thrombocytopenia and leukopenia on Day 87 after dose 1. Of these two SAEs, only the SAE of deep venous thrombosis required hospitalization.

Deaths

During the blinded phase of the study, there were four deaths in the vaccinated group, all of which were considered unrelated by the Sponsor and investigator, and 13 deaths in the placebo group, one of which was considered related by the Sponsor or investigator (respiratory distress). Of these four fatal events, three occurred following dose 1, and one had time to onset within 28 days of vaccination. A participant in the 18-59 years of age cohort experienced death from an unknown cause (reported as “unnatural death cause unknown”) on Day 25 after dose 1. A participant >80 years of age reported an SAE of lung adenocarcinoma Day 57 after dose 1 and died on Day 154. A participant in the ≥60 years of age cohort with a history of breast cancer and hypertension experienced an event of cerebral hemorrhage on Day 55 after dose 1. A participant in the 18-59 years of age cohort with a history of obesity, hypertension, and dyslipidemia experienced an SAE of myocardial infarction (reported as “suspected myocardial infarction”) on Day 90, 33 days after dose 2.

An additional four fatal events were reported after Ad26.COV2.S in the open-label phase, none of which were considered related, and all of which occurred more than 30 days following the most recent vaccination. A participant in the ≥60 years of age cohort experienced an overdose of heroin Day 51 after dose 1. A participant in the 18-59 years of age cohort with a history of COPD, obesity, type 2 diabetes mellitus, asthma, and hypertension experienced an event of chronic obstructive pulmonary disease on Day 62 after dose 1 and Day 5 after dose 2. A participant in the ≥60 years of age cohort experienced an event of COVID-19 pneumonia with onset 64 days after dose 2 and died 5 days later. Since this COVID-19 related death occurred during the open-label phase, it was not counted in the blinded-phase analyses of vaccine efficacy against severe/critical COVID-19, COVID-19 related hospitalizations, or COVID-19 related deaths. A participant in the 18-59 years of age cohort with a history of depression, type 2 diabetes mellitus, depression, excess alcohol consumption, chronic obstructive pulmonary disease (COPD), and pancreatitis experienced an event of death from an unknown cause on Day 96 after dose 1.

AEs leading to study withdrawal

Overall, there were 14 participants that experienced adverse events that led to study discontinuation (Ad26COV.2.S n=5 [0.1%], placebo n=9 [0.1%]).

4.5.1.4 Summary of Study COV3009 and Limitations

COV3009 provides VE data from a double-blind, placebo-controlled study where participants were administered 2 doses of Ad26.COV2.S at $5x10^{10}$ vp approximately 2 months after their primary dose. Although not independently confirmed by FDA from datasets, summaries of the data suggest there may be a benefit in a second dose administered approximately 2 months after the primary dose, when compared to the efficacy seen in the pivotal study COV3001. However, confidence intervals around the efficacy estimates for a single dose from COV3001 vs. 2 doses from COV3009 overlap. Additionally, the small sample size cases in individuals 60 years of age and older limits the ability to conclude about an increase in efficacy after the second dose in this group. Finally, the small number of accrued cases confirmed to be caused by the Delta variant precludes any conclusion regarding efficacy against that variant. Preliminary review of safety analyses following a second dose (2-month interval) among several thousand recipients with a median blinded follow-up of 36 days do not identify increased reactogenicity or new safety concerns compared with the safety profile of the single dose; however, post-authorization surveillance will be needed to further evaluate and quantify the risk of uncommon but medically important adverse reactions associated with the single-dose primary vaccination (e.g., TTS and GBS).

4.5.2 Study COV1001-Cohort 1a & Cohort 3

Immunogenicity and safety data from Study COV1001 from participants who were administered 2-doses of Ad26.COV2.S 2 months apart (Cohort 1a/Group 1) or 3 months apart (Cohort 2/Group 1) are provided below.

4.5.2.1 Design

Please see Section 4.4.1.

4.5.2.2 Immunogenicity

Cohort 1a, Group 1 (2 months interval)

In Cohort 1a, Group 1, immunogenicity data was available from 25 healthy adults between the ages of 18 and 55 who were administered 2 doses of Ad26.COV2.S at 5x1010 vp, 56 days apart. Immune response based on neutralizing antibody titers assessed by wtVNA against the Victoria/1/2020 reference strain at scheduled study time points are displayed in Table 32. All 25 participants had detectable neutralizing antibody titers starting 28 days post-dose 1, with a further slight increase in geometric mean titers when assessed at 56 days post-dose 1. There was a boost in immune response observed at 14 and 28 days post-dose 2, with geometric mean increase in titers of 13.9-fold and 14.9-fold above baseline, respectively, compared to 4.9-fold from baseline at Day 57. By Day 239 (6 months post-dose 2), there is noted to be a decrease in neutralizing antibody titers, but still 1.6-fold higher compared to the levels observed on Day 57.

Table 32. SARS-CoV-2 Neutralization Per Wild Type Virus Neutralization Assay VICTORIA/1/2020 (IC50), COV1001 Cohort 1a Group 1, Per Protocol Immunogenicity Set (Analyses Not Verified by FDA)

	Baseline (D1)	28 Days Post Dose 1 (D29)	Pre-Dose 2 (D57)	14 Days Post Dose 2 (D71)	28 Days Post Dose 2 (D85)	Day 239
N	25	25	25	24	24	24
Geometric mean (95% CI)	<LLOQ (<LLOQ, <LLOQ)	224 (168, 298)	228 (221, 376)	827 (651, 1052)	849 (664, 1086)	465 (348, 620)
Positive sample n (%) (95% CI)	3 (12%) (3, 31)	25 (100%) (86, 100)	25 (100%) (86, 100)	24 (100%) (86, 100)	24 (100%) (86, 100)	24 (100%) (86, 100)
Titer >100 n (%) (95% CI)	0 (0, 14)	19 (76%) (55, 91)	25 (100%) (86, 100)	24 (100%) (86, 100)	24 (100%) (86, 100)	24 (100%) (86, 100)
Geometric mean increase (95% CI) from baseline	n/a	3.8 (2.8, 5.0)	4.9 (3.7, 6.3)	13.9 (10.9, 17.7)	14.3 (11.2, 18.3)	7.8 (5.9, 10.4)
Geometric mean increase (95% CI) from Dose 2	n/a	n/a	n/a	2.9 (2.3, 3.8)	2.9 (2.1, 3.8)	1.6 (1.2, 2.0)
Responders n/N (%) (95% CI)	n/a	22/25 (88%) (69, 97)	24/25 (96%) (80, 100)	24/24 (100%) (86, 100)	24/24 (100%) (86, 100)	24/24 (100%) (86, 100)

Source: Table 102, interim-tlr-vac31518cov1001.pdf
Positive sample=detectable titer
Responder: <LLOQ to ≥LLOQ, or 4x LLOQ if ≥LLOQ

Cohort 3, Group 1 (3 months interval)

In Cohort 3, Group 1, immunogenicity data was available from 25 healthy adults 65 years of age and older who were scheduled to receive 2 doses of Ad26.COV2.S at $5x10^{10}$ vp, 56 days apart. However, due a study pause triggered by an SAE which occurred in study COV3001, all participants in this cohort except the 15 sentinel participants were not able to have the Day 57 visit within the protocol-specified window. The actual timing of dose 2 ranged from 86 to 107 days (median visit: Day 87). Immunogenicity results for this study group, as presented in Table 33, is based on a sensitivity analysis of the FAS population excluding the sentinel participants. The dose 2 visit is changed to D87 (from Day 57 per schedule) and subsequent study time points calculated based on days from D87.

All 25 participants had detectable neutralizing antibody titers starting 28 days post-dose 1, with a slight decrease in geometric mean titers when assessed at 3 months post-dose 1. There was a boost in immune response observed at 14 and 28 days post-dose 2, with geometric mean increase in titers of 15-fold and 17-fold above baseline, respectively, compared to 4.8-fold from baseline at Day 57.

Table 33. SARS-CoV-2 Neutralization Per Wild Type Virus Neutralization Assay VICTORIA/1/2020 (IC50), COV1001 Cohort 3 Group 1, Full Analysis Set (Analyses Not Verified by FDA)

	Baseline (D1)	28 Days Post Dose 1 (D29)	Pre-Dose 2 (D87)	14 Days Post Dose 2 (D100)	28 Days Post Dose 2 (D114)
N	25	25	21	21	21
Geometric mean (95% CI)	<LLOQ (<LLOQ,<LLOQ)	298 (200, 444)	242 (147, 399)	945 (578, 1546)	1067 (630, 1807)
Positive sample n (%) (95% CI)	2 (8%) (1, 26)	25 (100%) (86, 100)	20 (95%) (76, 100)	21 (100%) (84, 100)	21 (100%) (84, 100)
Titer >100 n (%) (95% CI)	1 (4%) (0, 20)	24 (96%) (80, 100)	18 (86%) (64, 97)	20 (95%) (76, 100)	20 (95%) (76, 100)
Geometric mean increase (95% CI) from baseline	n/a	4.8 (3.3, 6.9)	4.0 (2.6, 6.1)	15.0 (9.5, 23.8)	17.0 (10.4, 27.6)
Geometric mean increase (95% CI) from Dose 2	n/a	n/a	n/a	3.8 (2.5, 5.6)	4.3 (3.1, 5.8)
Responders n/N (%) (95% CI)	n/a	24/25 (96%) (80, 100)	20/21 (95%) (76, 100)	21/21 (100%) (84, 100)	21/21 (100%) (84, 100)

Source: Table 143, interim-tlr-vac31518cov1001.pdf
Positive sample=detectable titer
Responder: <LLOQ to ≥LLOQ, or 4x LLOQ if ≥LLOQ

4.5.2.3 Safety

Safety data from this study are not summarized in detail because no concerning AEs (e.g., SAEs) were reported, and study COV3009 (summarized above) provides safety analyses for a much larger number of subjects who received a second dose following a 2-month interval.

4.5.2.4 Summary for Study COV1001 for 2-doses with 2-, 3- month intervals

In COV1001, study participants received 2 doses of Ad26.COV2.S at 5x1010 vp 2 months apart (Cohort 1a, Group 1) or 3 months apart (Cohort 3, Group 1). In all groups, there was an increase in neutralizing antibody titers of at least 2-fold compared to pre-boost. It is difficult to compare the immune response across the different groups due to the differences in the ages of the participants in Cohort 1a (18-55 years) and Cohort 3: (≥65 years). It is also difficult to compare neutralizing antibody data from the 2-dose groups (2- or 3-month intervals) to the respective data from the 6-month booster group (Cohort 2a) because of differences in the assays used (wtVNA for Cohorts 1a and 3 and psVNA for Cohort 2a). Based on geometric mean titers of wtVNA at 28 days post-dose 2, participants in Cohort 3 Group 1 (3-dose interval) appear to have higher titers post-dose 2 compared to participants in Cohort 1a Group 1 (2-month interval) despite representing an older age group and similar pre-dose 2 GMTs between the cohorts, indicating a potentially more robust immune response with a 3-month interval compared to 2-months. Although not summarized in detail, based on the limited number of subjects in the study, there were no new concerning safety signals observed after a second dose administered at 2- or 3-months following the first dose. The immunogenicity data from COV1001 for the 2-dose groups (2- or 3- month intervals) presented in this section have not been independently verified by the FDA.

4.5.3 Study COV1002

4.5.3.1 Design

Study COV1002 is an ongoing randomized, double-blind, placebo-controlled Phase 1 non-U.S. IND study in Japan to assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels administered as a 2-dose schedule in healthy, immunocompetent adults aged 20 through 55 years and ≥65 years.

Table 34. Relevant Groups from COV1001 with Available Data (dose level for all doses is $5x10^{10}$ vp) (Analyses Not Verified by FDA)

Cohort	Group	Interval Between Dose 1 and Dose 2	Immunogenicity Data N Participants	Age of Participants (years)
1	1	3 months	51	20-55
2	1	2 months	50	≥65

4.5.3.2 Immunogenicity

Cohort 1, Group 1 (3 months interval)

In Cohort 1, Group 1, immunogenicity data was available from 51 healthy adults 20 through 55 years of age were scheduled to receive 2 doses of Ad26.COV2.S at $5x10^{10}$ vp, 56 days apart. Due to the global study pause triggered by an SAE in COV3001, participants in this cohort were not able to receive dose 2 and collect blood for immunogenicity within the scheduled 2 months window. The actual timing of the Day 57 vaccination and blood draw ranged from 73 to 88 days (median of 78 days). Table 35 shows a sensitivity analysis of immunogenicity results based on actual study day of vaccination.

All participants had detectable neutralizing antibody titers starting 28 days post-dose 1, with a further increase in geometric mean titers when assessed at 3 months post-dose 1. There was a boost in immune response observed at 14 and 28 days post-dose 2, with geometric mean increase in titers of 17.9-fold and 18.6-fold above baseline, respectively, compared to 8-fold from baseline at 3 months post-primary vaccination (pre-dose 2).

Table 35. SARS-CoV-2 Neutralization Wild Type VNA-VICTORIA/1/2020 (IC50), COV1002 Cohort 1 Group 1, PPI Set (Analyses Not Verified by FDA)

	Baseline (D1)	28 Days Post Dose 1 (D29)	Pre-Dose 2 (D78)	14 Days Post Dose 2 (D92)	28 Days Post Dose 2 (D85)
N	51	50	43	43	43
Geometric Mean (95% CI)	<LLOQ (<LLOQ, <LLOQ)	269 (228, 318)	469 (382, 576)	1049 (828, 1329)	1088 (817, 1449)
Positive Sample n (%) (95% CI)	1 (2%) (0, 10)	50 (100%) (93, 100)	43 (100%) (92, 100)	43 (100%) (92, 100)	43 (100%) (92, 100)
Titer >100 n (%) (95% CI)	0 (0, 7)	48 (96%) (86, 100)	42 (98%) (88, 100)	43 (100%) (92, 100)	43 (100%) (92, 100)
Geometric mean increase (95% CI) from Baseline	n/a	4.6 (3.9, 5.4)	8.0 (6.5, 9.8)	17.9 (14.2, 22.7)	18.6 (14.0, 24.7)
Geometric mean increase (95% CI) from Dose 2	n/a	n/a	n/a	2.2 (1.8, 2.8)	2.3 (1.8, 3.0)
Responders n/N (%) (95% CI)	n/a	49/50 (98%) (89, 100)	43/43 (100%) (92, 100)	43/43 (100%) (92, 100)	43/43 (100%) (92, 100)
≥4-fold n (%)	n/a	30 (60%)	38 (88%)	43 (100%)	43 (100%)

Source: Table 49, interim-csr-vac31518cov1002.pdf
Positive sample=detectable titer
Responder: <LLOQ to ≥LLOQ, or 4x LLOQ if ≥LLOQ

Cohort 2, Group 1 (2 months interval)

In Cohort 2, Group 1, immunogenicity data was available from 50 healthy adults 65 years of age and older who received 2 doses of Ad26.COV2.S at $5x10^{10}$ vp, 56 days apart. Analysis of immune response as measured by wtVNA is displayed in Table 36.

At 28 days post-dose 1 and through Day 57 (pre-dose 2), 98% of participants had detectable titers. There was a boost in immune response observed at 14 and 28 days post-dose 2, with geometric mean increase in titers of 8.7-fold and 7.4-fold above baseline, respectively, compared to 4.9-fold from baseline at 2 months post-primary dose (pre-dose 2).

Table 36. SARS-CoV-2 Neutralization Wild Type VNA-VICTORIA/1/2020 (IC50), COV1002 Cohort 2 Group 1, PPI Set (Analyses Not Verified by FDA)

	Baseline (D1)	28 Days Post Dose 1 (D29)	Pre-Dose 2 (D57)	14 Days Post Dose 2 (D71)	28 Days Post Dose 2 (D85)
N	50	50	49	48	48
Geometric Mean (95% CI)	<LLOQ (NE, NE)	311 (259, 374)	281 (204, 386)	504 (404, 627)	429 (335, 550)
Positive Sample n (%) (95% CI)	0	49 (98%) (89, 100)	48 (98%) (89, 100)	48 (100%) (93, 100)	48 (100%) (93, 100)
Titer >100 n (%) (95% CI)	0	48 (96%) (86, 100)	39 (80%) (66, 90)	47 (98%) (89, 100)	46 (96%) (86, 99)

	Baseline (D1)	28 Days Post Dose 1 (D29)	Pre-Dose 2 (D57)	14 Days Post Dose 2 (D71)	28 Days Post Dose 2 (D85)
Geometric mean increase (95% CI) from baseline	n/a	5.4 (4.6, 6.5)	4.9 (3.6, 6.7)	8.7 (7.0, 10.8)	7.4 (5.8, 9.5)
Geometric mean increase (95% CI) from dose 2	n/a	n/a	n/a	1.7 (1.3, 2.4)	1.5 (1.1, 2.0)
Responders n/N (%) (95% CI)	n/a	49/50 (98%) (89, 100)	48/49 (98%) (89, 100)	48/48 (100%) (93, 100)	48/48 (100%) (93, 100)
≥4-fold n (%)	n/a	34 (68%)	25 (51%)	38 (79%)	36 (75%)

Source: Table 58, interim-csr-vac31518cov1002.pdf
Positive sample=detectable titer
Responder: <LLOQ to ≥LLOQ, or 4x LLOQ if ≥LLOQ

Even accounting for differences in pre-dose 2 GMT that could affect post-dose 2 GMT, the geometric mean increase from pre-dose 2 to post-dose 2 in this group appears to be marginally lower compared to that seen in Cohort 1, Group 1. However, it is difficult to disentangle whether this may be due to the differences in age of the two groups (Cohort 1 consisted of participants 20-55 years of age while Cohort 2 consisted of participants ≥65 years of age) or due to the longer dosing interval in Cohort 1 compared to Cohort 2.

4.5.3.3 Safety

One SAE was reported as of the cutoff date of December 28, 2020 in Cohort 1, Group 1. A 21-year-old man with no significant medical history experienced sudden hearing loss in one ear starting 34 days after dose 1. The participant was later hospitalized for treatment of hearing loss and the event was reported as resolved by Day 70. Workup for his sensorineural hearing loss including laboratory tests and imaging did not reveal an etiology. This SAE was considered not related by the investigator. Additional safety data from this study are not summarized in detail because study COV3009 (summarized above) provides safety analyses for a much larger number of subjects who received a second dose following a 2-month interval.

4.5.3.4 Summary of Study COV1002 and Limitations

Based on a small number of subjects in this Phase 1 study, an increase in immune response as measured by wtVNA against the reference strain is noted when a second dose is given at either 2 or 3 months after the first dose, with a marginally higher response (relative to pre-dose 2) observed in 3 months interval group compared to the 2 months interval group. Although not summarized in detail, based on the limited number of subjects in the study, there were no new concerning safety signals observed after a second dose administered at 2- or 3-months following the first dose. The immunogenicity data from COV1002 (2- or 3- month intervals) presented in this section have not been independently verified by the FDA. Limitations also include that this non-U.S. IND study was conducted in a small homogenous population, and results may not be generalizable to all populations.

4.5.4 Study COV2001

4.5.4.1 Design

Study COV2001 is an ongoing randomized, double-blind, placebo-controlled, multicenter, Phase 2a study that included among enrolled participants healthy adults aged 18 through 55 years and adults aged 65 years and older in good or stable health. The study evaluated the safety and immunogenicity of Ad26.COV2.S given as a single dose or as 2 doses 2-3 months apart. All participants in the study were given a dose of Ad26.COV2.S at Month 6 to assess

anamnestic response. Neutralizing antibody data from after Month 6 in relevant study groups are not yet available.

Table 37. Relevant Groups from COV2001 With Available Data (Dose Level for All Doses Is $5x10^{10}$ vp) (Analyses Not Verified by FDA)

Group	Interval Between Dose 1 and Dose 2	Immunogenicity Data N Participants	Age of Participants (years)
1	2 months	38	18-55; ≥65
9	3 months	37	18-55; ≥65

4.5.4.2 Immunogenicity

Group 1 (2 months interval)

In Group 1, immunogenicity data was available from 38 participants who received 2 doses of Ad26.COV2.S at $5x10^{10}$ vp, 56 days apart. Analysis of immune response as measured by wtVNA is displayed in Table 38.

At 2 months post-dose 1, 87% of participants had detectable titers. There was a boost in immune response observed at 14 and 28 days post-dose 2, with geometric mean increase in titers of 8.8-fold and 7.4-fold above baseline, respectively, compared to 3.7-fold from baseline at 2 months post-dose 1 (pre-dose 2).

Table 38. SARS-CoV-2 Neutralization Wild Type VNA-VICTORIA/1/2020 (IC50), COV2001 Group 1, PPI Set (Analyses Not Verified by FDA)

	Baseline (D1)	28 Days Post-Dose 1 (D29)	Pre-Dose 2 (D57)	14 Days Post-Dose 2 (D71)	28 Days Post-Dose 2 (D85)
N	38	39	39	39	38
Geometric Mean (95% CI)	<LLOQ (<LLOQ, <LLOQ)	260 (196, 346)	212 (142, 314)	518 (354, 758)	424 (301, 597)
Positive Sample n (%) (95% CI)	1 (2.6%) (0.1, 13.8)	37 (94.9%) (82.7, 99.4)	34 (87.2%) (72.6, 95.7)	38 (97.4%) (86.5, 99.9)	36 (94.7%) (82.3, 99.4)
Titer >100 n (%) (95% CI)	0	33 (84.6%) (69.5, 94.1)	28 (71.8%) (55.1, 85.0)	37 (94.9%) (82.7, 99.4)	35 (92.1%) (78.6, 98.3)
Geometric mean increase (95% CI) from baseline	n/a	4.4 (3.3, 5.7)	3.7 (2.6, 5.2)	8.8 (6.1, 12.8)	7.4 (5.4, 10.2)
Geometric mean increase (95% CI) from dose 2	n/a	n/a	n/a	2.3 (1.7, 3.1)	1.8 (1.4, 2.4)
Responders n/N (%) (95% CI)	n/a	36/38 (94.7%) (82.3, 99.4)	33/38 (86.8%) (71.9, 95.6)	37/38 (97.4%) (86.2, 99.9)	35/37 (94.6%) (81.8, 99.3)

Source: Table 64, pa-tlr-vac31518cov2001.pdf
Positive sample=detectable titer
Responder: <LLOQ to ≥LLOQ, or 4x LLOQ if ≥LLOQ

Group 9 (3 months interval)

In Group 9, immunogenicity data was available from 37 participants who received 2 doses of Ad26.COV2.S at $5x10^{10}$ vp, 3 months apart. Analysis of immune response as measured by wtVNA is displayed in Table 39.

At 3 months post-dose 1, 97% of participants had detectable titers. There was a boost in immune response observed at 14 and 28 days post-dose 2, with geometric mean increase in

titers of 15.6-fold and 12.2-fold above baseline, respectively, compared to 4.1-fold from baseline at 3 months post-dose 1 (pre-dose 2).

The immune response after a second dose in Group 9 with a 3-month interval appears to be higher compared to that seen after a second dose in Group 1 with a 2-month interval. However, these results are based on a small sample size, with overlapping confidence intervals.

Table 39. SARS-CoV-2 Neutralization Wild Type VNA-VICTORIA/1/2020 (IC50), COV2001 Group 9, PPI Set (Analyses Not Verified by FDA)

	Baseline (D1)	Pre-Dose 2 (D85)	14 Days Post Dose 2 (D99)	28 Days Post Dose 2 (D113)
N	37	35	34	37
Geometric Mean (95% CI)	<LLOQ	236 (169, 328)	904 (691, 1184)	694 (473, 1018)
Positive Sample n (%) (95% CI)	0	34 (97.1%) (85.1, 99.9)	34 (100%) (89.7, 100)	36 (97.3%) (85.8, 99.9)
Titer >100 n (%) (95% CI)	0	29 (82.9%) (66.4, 93.4)	34 (100%) (89.7, 100)	35 (94.6%) (81.8.99.3)
Geometric mean increase (95% CI) from Baseline	n/a	4.1 (3.0, 5.7)	15.6 (11.9, 20.4)	12.2 (8.4, 17.6)
Geometric mean increase (95% CI) from Dose 2	n/a	n/a	3.7 (2.6, 5.3)	2.9 (2.0, 4.3)
Responders n/N (%) (95% CI)	n/a	34/35 (97.1%) (85.1, 99.9)	34/34 (100%) (89.7, 100.0)	36/37 (97.3%) (85.8, 99.9)

Source: Table 65, pa-tlr-vac31518cov2001.pdf
Positive sample=detectable titer
Responder: <LLOQ to >LLOQ, or 4x LLOQ if >LLOQ

4.5.4.3 Safety

Two thrombotic events were reported in this study. One participant had thrombophlebitis one day after dose 1 of $5x10^{10}$ vp of Ad26.COV2.S and one participant in Group 1 had Grade 3 ischemic stroke 8 days after the $1.25x10^{10}$vp dose on Month 6. No further details were provided for these cases. Additional safety data from this study are not summarized in detail because study COV3009 (summarized above) provides safety analyses for a much larger number of subjects who received a second dose following a 2-month interval.

4.5.4.4 Summary for Study COV2001 and Limitations

Based on a small number of subjects in this Phase 2 study, an increase in immune response as measured by wtVNA against the reference strain is noted when a second dose is given at either 2 or 3 months after the first dose, with a numerically higher response observed after the 3-month interval compared to the 2-month interval. Although this study enrolled participants who were 18-55 years and those who were >65 years, the demographic breakdown by age of participants who contributed immunogenicity data to the analyses shown are not available. Differences in age of participants between the two groups may impact the results seen. Although not summarized in detail, based on the limited number of subjects in the study, there were no new concerning safety signals observed after a second dose administered at 2- or 3-months following the first dose. The immunogenicity data from COV1002 (2- or 3- month intervals) presented in this section have not been independently verified by the FDA.

5 Pharmacovigilance Activities

The Sponsor's pharmacovigilance plan (PVP) includes the following safety concerns:

- Important identified risks: Anaphylaxis; Thrombosis with thrombocytopenia syndrome (TTS); Guillain-Barré syndrome (GBS)
- Important potential risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease; Venous thromboembolism; Immune thrombocytopenia (ITP)

Areas of missing information include the following: use during pregnancy; use in breastfeeding women; 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, cardiovascular disorders); interaction with other vaccines; long-term safety; use in pediatric age groups.

The Sponsor conducts passive and active surveillance to monitor the post-authorization safety for the Janssen COVID-19 Vaccine, including:

- Mandatory reporting by the Sponsor of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days: serious adverse events (AEs) (irrespective of attribution to vaccination); COVID-19 disease resulting in hospitalization or death; Multisystem Inflammatory Syndrome (MIS)
- Periodic aggregate review of safety data including assessment of adverse events; vaccine administration errors, whether or not associated with an adverse event; and newly identified safety concerns.
- Post-authorization observational studies, that would be modified to encompass the evaluation of a booster dose, include a pregnancy registry and active surveillance safety studies using large US health insurance claims and/or electronic health record database(s)

6 Topic for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on October 15, 2021, to discuss:

- Whether the data presented by Janssen support the safety and effectiveness of Janssen COVID-19 Vaccine for emergency-authorized use as a booster dose at least 2 months after a single-dose primary vaccination, and
- Whether the data presented by Janssen support that an interval of at least 6 months between the primary vaccination and booster dose may result in a more robust booster response.

7 References

[1] Woo EJ, Mba-Jonas A, Dimova RB, Alimchandani M, Zinderman CE, Nair N. Association of Receipt of the Ad26.COV2.S COVID-19 Vaccine With Presumptive Guillain-Barré Syndrome, February-July 2021. JAMA. Published online October 07, 2021. doi:10.1001/jama.2021.16496
[2] Federal Food Drug and Cosmetic Act. 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011). 2011.
[3] FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/media/139638/download
[4] FDA. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. February 2021. https://www.fda.gov/media/142749/download
[5] FDA. Emergency Use Authorization Review Memorandum for the Janssen COVID-19 Vaccine/. Ad26.COV2.S. December 11, 2020. https://www.fda.gov/media/146338/download