Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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SUPPLEMENTARY METHODS

Changes in Conduct and Protocol Amendments

There were 6 amendments to the protocol before the final analysis. The first amendment to the protocol was adopted before any study-related procedures began.

In the first amendment (15 September 2020), the time to begin counting Covid-19 cases after vaccination was decreased from ≥28 days post-vaccination to ≥14 days post-vaccination (primary endpoint). Other changes included the following: implementation of the selected dose level of 5×10^{10} vp for Ad26.COV2.S based on data from the first-in-human study VAC31518COV1001; additional changes based on emerging epidemiology information and advancing insights, including the determination of the sample size, further details of the case definitions for Covid-19, and the addition of target percentages (min/max) for enrollment of certain age groups; changes made in response to feedback received from Health Authorities, partners, and the community; and some minor editorial changes.

The second amendment (29 October 2020) included the following changes: clarification that all participants who have a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) positive finding for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), even if asymptomatic, will be followed until there are 2 consecutive negative RT-PCR tests; correction of errors, including the clarification that blood will be drawn on day 29 for biomarker RNAseq analyses (PAXgene tube), which is needed to assess the current objectives; and minor editorial changes.

The third amendment (14 December 2020) included the following changes: the occurrence of molecularly confirmed, moderate to severe–critical Covid-19, with onset at least 28 days post-vaccination was added as a co-primary endpoint in addition to the current primary endpoint counting as of 14 days post-vaccination. The applicable secondary and exploratory endpoints were updated similarly to also include Covid-19 cases with onset at least 28 days post-vaccination. In addition, the total sample size was reduced from 60,000 to approximately 40,000 participants. The protocol was further amended to change the conditions for monitoring whether efficacy greater than 30% is achieved using the sequential monitoring algorithm: (1) the need for a follow-up of 8 weeks for 50% of the participants prior to an initial look at an efficacy signal if the other conditions are met was removed, (2) the minimum number of Covid-19 cases meeting the primary case definition needed to start the efficacy monitoring was modified to at least 42 instead of 20 to increase the robustness of the package in case of an early efficacy signal. Furthermore, additional secondary and exploratory objectives and endpoints were added; the Clinical Evaluation Committee was replaced by the Clinical Severity Adjudication Committee; the definitive role of the Clinical Severity Adjudication Committee in defining the severity of cases of Covid-19 was clarified; the utilization of tokenization and matching procedures was added; clarification of procedures for unblinding of study participants who may become eligible to receive an authorized/licensed Covid-19 vaccine during the course of the study was included; and additional clarifications and minor editorial changes were added.

The introduction of co-primary endpoints at ≥14 and ≥28 days post-vaccination in amendment 3 was done because it was recognized from preclinical and human immunology results that protection and human immune responses might occur as early as day 14. It was also recognized that, as immune response matured, higher levels of protection might be achieved. Therefore, to capture these 2 concepts, the co-primary endpoints were introduced. The sample size was reduced because the incidence of Covid-19 was substantially higher than assumed at the time of protocol planning. Based on the observed incidence and modeling, there was a high degree of probability that an efficacy signal meeting the prespecified criteria in the amendment would be reached at or before the time at which 50% of participants would have been followed for 8 weeks post-vaccination.

The fourth amendment (22 February 2021) outlined procedures to be followed after Emergency Use Authorization (EUA), conditional licensure, or approval in any country where a single dose of Ad26.COV2.S vaccine will be offered to enrolled participants who initially received placebo, resulting in de facto unblinding of participants and investigators. The following changes were included: at the unblinding/month 6 visit, all participants who initially received placebo will be offered a single dose of Ad26.COV2.S (5×10^{10} vp), starting an open-label phase of the study (occurring as soon as possible after the day 71 visit) with a blood draw and nasal swab at unblinding/month 6 for all participants; clarification that RT-PCR tests obtained from any source will be used for all analyses, including RT-PCR test performed by local laboratories, without requiring confirmation by the central laboratory as part of any of the case definitions.

The fifth amendment (7 May 2021) included additional safety measures due to reports of adverse events following use of the Ad26.COV2.S vaccine under EUA in the United States, suggesting an increased risk of thrombosis combined with thrombocytopenia. The following changes were included: thrombosis with thrombocytopenia was to be followed as an adverse event of special interest requiring reporting to the sponsor within 24 hours; collection of blood samples for baseline assessment of platelet count and storage for coagulation-related testing; anaphylaxis was added as an important identified risk; reinstatement of the use of a central laboratory for RT-PCR tests or other molecular diagnostic tests to confirm cases of SARS-CoV-2 infection upon health authority request.

The sixth amendment (4 September 2021) included a 1-dose booster vaccination with Ad26.COV2.S (5×10^{10} vp) to be offered to all ongoing participants in the study, regardless of primary vaccination regimen (Ad26.COV2.S vaccine or a single- or 2-dose regimen of an mRNA vaccine or another authorized Covid-19 vaccine including protein, inactivated, and adenovector based vaccines). The booster vaccination will be administered in the open-label phase of the study. The combination of homologous or heterologous prime/boost vaccination will not be randomized but depends on what participants received during the double-blind phase of the study. Booster vaccination should occur preferably 6 months but at least 3 months after primary vaccination. Participants in the study who received an additional Covid-19 vaccination after the primary regimen outside the study with any vaccine will also be eligible for the Ad26.COV2.S booster in this study. Participants are free to choose when to receive the booster vaccination within the window of the booster vaccination visit, to receive booster vaccination outside the study, or not to receive a booster. Participants who choose to receive a booster vaccination with the Ad26.COV2.S vaccine (if recommended and available) or another

authorized Covid-19 vaccine outside the study or who choose not to receive a booster vaccination will not be withdrawn from the study and will be encouraged to remain in the study. All participants who received a booster vaccination within the study or received a booster vaccination outside the study and remained in the study will be monitored for safety, immunogenicity, and efficacy. With implementation of this amendment, the start date of the first crossover unblinding visit (implemented with Amendment 4) and the date of first booster vaccine administration until 1-year follow-up of the last booster vaccination define the open-label booster vaccination phase of the study. This phase will be utilized to describe safety, immunogenicity, and efficacy during the time participants have and have not been boosted.

Study Pause

A committee consisting of the representatives of the sponsor and collaboration partners, along with the principal investigator (the protocol safety review team) and the Janssen Medical Safety Council monitored safety in a blinded manner, including the study vaccination pausing rules (applicable to Stages 1a and 2a only). If a study vaccination was considered to raise significant safety concerns (and a specific set of pausing criteria had been met), further vaccination of participants was paused. On 11 October 2020, the sponsor was informed of a serious adverse event (SAE) in Study COV3001 that met a study pausing rule. As a precautionary measure, vaccinations in all studies in the program were paused. After data and safety monitoring board (DSMB) review, resumption of study vaccinations from 27 October 2020 was recommended.

Trial Sponsor and Collaborators

ENSEMBLE is a collaboration between the sponsor, Janssen Research and Development (an affiliate of Janssen Vaccines and Prevention, a Janssen pharmaceutical company acquired by Johnson & Johnson), and the Biomedical Advanced Research and Development Authority, the National Institutes of Health, Covid-19 Prevention Network, and the Department of Defense.

Ethics

All participants provided written informed consent. The trial adheres to Declaration of Helsinki principles and International Conference on Harmonisation Good Clinical Practice guidelines; the protocol and amendments were approved by institutional review boards per local regulations. An independent DSMB (unblinded) continuously monitors safety, including for vaccine-associated enhanced respiratory disease.

Inclusion and Exclusion Criteria

Every potential participant must have satisfied all of the following criteria to be enrolled in the study: participant must provide consent indicating that he or she understands the purpose, procedures, and potential risks and benefits of the study and is willing to participate in the study; participant must be willing and able to adhere to the prohibitions and restrictions specified in the protocol; for Stages 1a and 1b, participant must be ≥18 to <60 years of age on the day of signing the informed consent form (ICF); for Stages 2a and 2b, participants must be ≥60 years of

age on the day of signing the ICF; for Stages 1a and 2a, in the investigator's clinical judgment, the participant must be in either good or stable health, including a body mass index (BMI) <30 kg/m^2.

Participants in Stages 1a and 2a may have underlying illnesses (not associated with increased risk of progression to severe Covid-19), as long as their symptoms and signs are stable and well controlled. If participants are on medication for a condition not part of the comorbidities listed in the full protocol available online, the medication dose cannot have been increased within 12 weeks preceding vaccination and is expected to remain stable for the duration of the study. Participants would be included on the basis of relevant medical history and BMI measurement at screening.

For Stages 1b and 2b, in the investigator's clinical judgment, participants may have had a stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe Covid-19 (e.g., stable/well-controlled HIV infection). If participants were on medication for a medical condition (including comorbidities associated with an increased risk of progression to severe Covid-19), the medication dose cannot have been increased within 12 weeks preceding vaccination and must be expected to remain stable for the duration of the study. Participants would be included on the basis of relevant medical history and BMI measurement at screening.

Participants with HIV infection must have had documented stable/well-controlled infection, defined as documented CD4 cell count ≥300 cells/µL within 6 months prior to screening, and documented HIV viral load <50 copies/mL within 6 months prior to screening. Participants with HIV must have been on a stable anti-retroviral treatment (ART) for 6 months (unless the change was due to tolerability, in which case the regimen could be for only the previous 3 months; changes in formulation were allowed; nationwide guidelines that require transition from one ART regimen to another were allowed) and the participant must have been willing to continue his/her ART throughout the study as directed by his/her local physician.

Before randomization, participants must be either not of childbearing potential, or of childbearing potential and practicing an acceptable effective method of contraception and agree to remain on such a method of contraception from providing consent until 3 months after administration of study vaccine. Use of hormonal contraception should have started at least 28 days before the administration of study vaccine. All participants of childbearing potential must have had a negative highly sensitive urine pregnancy test at screening and a negative pregnancy test on the day of and prior to study vaccine administration.

Participants must have agreed to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving the study vaccine.

Any potential participant who meets any of the following criteria would be excluded from participating in the study: participant has a clinically significant acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned study vaccination (randomization at a later date was permitted at the discretion of the investigator and after consultation with the

sponsor); has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine); has abnormal function of the immune system resulting from clinical conditions (e.g., autoimmune disease or potential immune-mediated disease or known or suspected immunodeficiency, or hemodialysis) expected to have an impact on the immune response of the study vaccine.

Participants with clinical conditions stable under non-immunomodulator treatment (e.g., autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could be enrolled at the discretion of the investigator. Non-immunomodulator treatment was allowed as well as steroids at a non-immunosuppressive dose or route of administration.

Participants were excluded if they had chronic or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose was considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent. Ocular, topical, or inhaled steroids were allowed.

Participants were excluded if they received antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of study vaccine and during the study; received treatment with immunoglobulin in the 3 months or exogenous blood products (autologous blood transfusions are not exclusionary) in the 4 months before the planned administration of the study vaccine or had any plans to receive such treatment during the study; received or planned to receive licensed live attenuated vaccines within 28 days before or after planned administration of study vaccine; received or planned to receive other licensed (not live) vaccines within 14 days before or after planned administration of study vaccine; previously received a coronavirus vaccine; received an investigational drug (including investigational drugs for prophylaxis of Covid-19) within 30 days or used an invasive investigational medical device within 30 days or received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for Covid-19 treatment within 4 months or received an investigational vaccine (including investigational adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine or were currently enrolled or planned to participate in another investigational study during the course of this study. Participation in an observational clinical study was allowed at the investigator's discretion.

Efforts were made to ensure inclusion of participants who have not been previously enrolled in coronavirus studies and to prevent participants from subsequently enrolling in other coronavirus studies during their participation in this study. The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S was disallowed at any time prior to vaccination and during the study, except under the conditions described in the full protocol available online.

Participants were excluded if they were pregnant or planning to become pregnant within 3 months after study vaccine administration; had a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of

the investigator, participation would not be in the best interest of the participant (e.g., compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments; had a contraindication to intramuscular injections and blood draws (e.g., bleeding disorders); had major psychiatric illness that in the investigator's opinion would compromise the participant's safety or compliance with the study procedures; could not communicate reliably with the investigator; were, in the opinion of the investigator, unlikely to adhere to the requirements of the study, or were unlikely to complete the full course of vaccination and observation.

Exclusion criteria for Stages 1a and 2a included comorbidities that were or might be associated with an increased risk of progression to severe Covid-19, i.e., moderate to severe asthma; chronic lung diseases such as chronic obstructive pulmonary disease (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension; moderate to severe high blood pressure; obesity (BMI $\geq$30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end-stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; and sleep apnea; history of or current Parkinson's disease; seizures; ischemic strokes; intracranial hemorrhage; encephalopathy and meningoencephalitis; history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence); history of acute polyneuropathy (e.g., Guillain-Barré syndrome); surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization, or had surgery requiring hospitalization planned during the time the participant was expected to participate in the study or within 6 months after study vaccine administration; or had chronic active hepatitis B or hepatitis C infection per medical history.

Study Procedures for Reporting Symptoms of Covid-19 and Collection of Swabs

Participants were provided with a pulse oximeter, a swab self-collection kit, as well as a device or an application on their own device to enter study required data. Participants responded to a question twice per week assessing if they had symptoms, and if "yes" they were experiencing symptoms they immediately were prompted to completed the Symptoms of Infection with Coronavirus-19 (SIC) questionnaire (a measure of symptom severity developed per best practice),[1] and enter their pulse oximetry results. Those with symptoms completed the SIC daily and took pulse oximeter readings 3 times daily from the day symptoms began for the duration of illness. Based on the SIC, investigators contacted participants on the day or day after symptoms began to assess whether the symptoms qualified as suspected Covid-19. Participants took nasal swabs at home on the day or day after symptoms began and every other day until there were 2 consecutive negative swabs; in addition, study staff took nasal swabs at least once. Swabs were refrigerated in sterile saline and stored in a freezer before shipment to the central laboratory on dry ice.

Efficacy Assessments

Key secondary and exploratory endpoints were evaluated, including vaccine efficacy against severe–critical Covid-19, symptomatic Covid-19, asymptomatic infection, any SARS-CoV-2 infection (molecularly or serologically confirmed) medical intervention (included hospitalization as adjudicated by committee, intensive care unit admission, mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomography [CT] findings), viral load, and infection in participants with comorbidities associated with increased risk of severe Covid-19 (**Supplementary Table 1**). Vaccine efficacy against variants was also evaluated for the primary and key secondary endpoints. The double-blind phase was defined as time since vaccination until the date of unblinding, study discontinuation, or the last available timepoint (whichever occurred first).

Safety Definitions

Serious adverse events included those that resulted in death, were life-threatening, required hospitalization (or prolonging of existing hospitalization), resulted in persistent or significant disability, were congenital anomalies, were a suspected transmission of any infectious agent via a medicinal product, or were considered medically important based on investigator judgment. Medically attended adverse events (MAAEs) included adverse events requiring hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. New onset of chronic diseases was collected as part of the MAAEs. Routine study visits were not considered medically attended visits.

In the subset of participants recording solicited local and systemic adverse events, solicited local adverse events included injection-site pain/tenderness, erythema, and swelling at the injection site. The largest diameter of any erythema and swelling was measured and recorded daily. Solicited systemic events included fatigue, headache, myalgia, nausea, and temperature monitoring for fever.

Covid-19 Case Definitions

Molecular confirmation of SARS-CoV-2 infection by a central laboratory (University of Washington Virology laboratory) was used for case definition analysis. A SARS-CoV-2–positive RT-PCR (Abbot) test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample was required for each case definition.

Moderate Covid-19 cases were defined by (1) a positive RT-PCR test for SARS-CoV-2 and (2) 2 or more of the following symptoms (new or worsening): fever or chills, cough, heart rate ≥90 beats/minute, muscle or body pain, headache, new loss of taste or smell, sore throat, red or bruised-looking feet or toes, nausea, vomiting, or diarrhea; or 1 or more of the following signs or symptoms: shortness of breath, respiratory rate >20 breaths/minute, clinical or radiologic evidence of pneumonia, deep vein thrombosis, or abnormal oxygen saturation (but above 93%).

Severe–critical Covid-19 cases were defined by a positive RT-PCR test for SARS-CoV-2 with 1 of the following features: respiratory failure; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors); respiratory rate >30 breaths/minute; heart rate ≥125 beats/minute; oxygen saturation of 93% or less (ambient air at sea level), or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen <300 mm Hg; intensive care unit admission; significant acute renal, hepatic, or neurologic dysfunction, or death.

Mild Covid-19 cases were defined by a positive RT-PCR test for SARS-CoV-2 and at any time during observation, 1 of the following symptoms, but not meeting the definition for moderate or severe–critical Covid-19: fever (≥38.0°C or ≥100.4°F), sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, muscle pain (myalgia), gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, new or changing olfactory or taste disorders, red or bruised-looking feet or toes, or shaking chills or rigors.

Symptoms of Infection with Coronavirus-19

"The following questions ask about symptoms people with coronavirus-19 infection may experience. Answer each question carefully by choosing 'yes' if you have experienced the symptom or 'no' if you have not experienced the symptom in the last 24 hours, If you choose 'yes', select the rating that best matches your experience."

In the last 24 hours, have you experienced…	Please rate the severity of each symptom you experienced.
Feeling generally unwell (run down) ☐ **Yes** ☐ **No** If yes, →	How severe was your **feeling (generally unwell or run down)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Fatigue (tiredness) ☐ **Yes** ☐ **No** If yes, →	How severe was your **fatigue (tiredness)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Physical weakness ☐ **Yes** ☐ **No** If yes, →	How severe was your feeling of **physical weakness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Cough ☐ **Yes** ☐ **No** If yes, →	How severe was your **cough** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Shortness of breath (difficulty breathing) ☐ **Yes** ☐ **No** If yes, →	How severe was your **shortness of breath (difficulty breathing)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Sore throat ☐ **Yes** ☐ **No** If yes, →	How severe was your **sore throat** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Nasal congestion (stuffy nose) ☐ **Yes** ☐ **No** If yes, →	How severe was your **nasal congestion (stuffy nose)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Wheezing (whistling sound while breathing) ☐ **Yes** ☐ **No** If yes, →	How severe was your **wheezing (whistling sound while breathing)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

In the last 24 hours, have you experienced…	Please rate the severity of each symptom you experienced.
Runny nose ☐ **Yes** ☐ **No** If yes, →	How severe was your **runny nose** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Sneezing ☐ **Yes** ☐ **No** If yes, →	How severe was your **sneezing** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chest congestion (mucus in chest) ☐ **Yes** ☐ **No** If yes, →	How severe was your **chest congestion (mucus in chest)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chest pain/ pressure/tightness ☐ **Yes** ☐ **No** If yes, →	How severe was your **chest pain/pressure/tightness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Muscle aches/pains ☐ **Yes** ☐ **No** If yes, →	How severe were your **muscle aches or pains** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Joint aches/pains ☐ **Yes** ☐ **No** If yes, →	How severe were the **aches or pains in your joints** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Headache ☐ **Yes** ☐ **No** If yes, →	How severe was your **headache** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Feeling faint ☐ **Yes** ☐ **No** If yes, →	How severe was your **feeling of faintness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Problems thinking clearly/brain fog ☐ **Yes** ☐ **No** If yes, →	How severe were your **problems thinking clearly/brain fog** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

In the last 24 hours, have you experienced…	Please rate the severity of each symptom you experienced.
Chills ☐ **Yes** ☐ **No** If yes, →	How severe were your **chills** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Skin rash ☐ **Yes** ☐ **No** If yes, →	How severe was your **skin rash** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Eye irritation/discharge ☐ **Yes** ☐ **No** If yes, →	How severe was your **eye irritation/discharge** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Diarrhea ☐ **Yes** ☐ **No** If yes, →	How severe was your **diarrhea** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Vomiting ☐ **Yes** ☐ **No** If yes, →	How severe was your **vomiting** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Nausea ☐ **Yes** ☐ **No** If yes, →	How severe was your **nausea** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Abdominal/ stomach pain ☐ **Yes** ☐ **No** If yes, →	How severe was your **abdominal/stomach pain** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Loss of appetite ☐ **Yes** ☐ **No** If yes, →	How severe was your **loss of appetite** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

What was your **highest temperature** in the last 24 hours? ____ °C/°F

What method did you use to take your temperature?

☐ **oral** ☐ **armpit** ☐ **ear** ☐ **forehead** ☐ **rectal**

In the last 24 hours, have you experienced...
Uncontrollable body shaking/shivering* ☐ **Yes** ☐ **No**
Decreased sense of smell* ☐ **Yes** ☐ **No**
Decreased sense of taste* ☐ **Yes** ☐ **No**
Red or bruised looking feet or toes* ☐ **Yes** ☐ **No**

*Please rate the severity of your symptoms in the last 24 hours?

☐ No Symptoms

☐ Mild

☐ Moderate

☐ Severe

Clinical Severity Adjudication Committee

The role of the Clinical Severity Adjudication Committee (CSAC) changed after the primary analysis; they reviewed the severity of all cases in the study and the reasoning for a severe classification, except for cases already adjudicated as severe, as a supplement to the algorithm described in the SAP. The CSAC also reviewed cases requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) and the onset of cases, taking into account all available relevant information at the time of adjudication. All fatal cases were sent to the CSAC for evaluation of possible Covid-19 related death. Re-adjudication occurred if new information became available. The last adjudication for a given case determined the status of the case for analysis. The CSAC's assessment was considered the definitive classification of the case.

Laboratory Methods

Reverse Transcriptase Polymerase Chain Reaction Testing

Diagnostic molecular RT-PCR testing for SARS-CoV-2 infection was performed using a nasal swab collected before vaccination on trial day 1 and during symptomatic infection. Molecular

confirmation of SARS-CoV-2 infection and viral load quantification was performed using the Abbott RealT*ime* SARS-CoV-2 RT-PCR at the Virology Laboratory of the University of Washington. SARS-CoV-2 seropositivity was evaluated using a nucleocapsid (N) immunoassay (Elecsys®, Roche) at trial entry and days 29 and 71, and at the unblinding/crossover visit. Assays were performed per manufacturers' protocols.

Sequencing Methods

Next-generation sequencing was performed using the Swift Biosciences SNAP Version 2.0, performed at the Virology Laboratory of the University of Washington, Department of Laboratory Medicine and Pathology (UW Virology). The SNAP assay utilizes multiple overlapping amplicons in a single tube to prepare ready-to-sequence libraries. Primer pairs used in SNAP are designed for generating libraries from first- or second-strand cDNA produced from viral isolates or clinical specimens and enabled successful SARS-CoV-2 library preparation from samples with low viral titers. The Swift Biosciences SARS-CoV-2 Version 2.0 kit (Catalog # CovGl V2-96) has been optimized to achieve additional genome coverage. The assay is optimized for Illumina sequencing platforms. A full clinical validation with determination of analytical sensitivity and specificity, limit of detection, accuracy, and assay precision (reproducibility and repeatability) has been performed.

Only S gene information was considered, and whole viral genome sequences have not yet been analyzed. However, the assignment of approximate lineages based on the predefined set of S amino acid substitutions agreed with the known circulating lineages in the considered countries based on the GISAID database (GISAlD 2021). To classify SARS-CoV-2 S sequences into their most probable lineages, the following predefined substitution profiles were used:

- B.1.1.7 – Alpha - H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,T716I,S982A,D1118H·
- B.1.351 – Beta – K417N,E484K,N501Y,D614G, A701V
- B.1.617.2/AY.1/AY.2 – Delta – L452R,T478K,D614G,P681R·
- B.1.427/429 – Epsilon – W152C,L452R,D614G·
- B.1.525 - Eta - A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L·
- P.1 – Gamma - K417T,E484K,N501Y,D614G,H655Y·
- B.1.526 – Iota - L5F,T95I,D253G,D614G,E484K, A701V·
- B.1.617.1 – Kappa - G142D,E154K,L452R,E484Q,D614G,P681R·
- C.37 – Lambda - R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N·
- P.3 – Theta - L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F
- P.2 – Zeta - E484K,D614G,V1176F (and not P.1, not P.3)·
- B.1.621 - T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N·
- C.36.3 - W152R,R346S,L452R,D614G,Q677H,A899S·
- R.1 - W152L,E484K,D614G,G769V·
- B.1.1.519 - T478K, D614G,P681H,T732A

- B.1/B.1.2/B.1.1/B.1.1.214 - D614G (not any other variant)

At the time of the trial, sequences categorized as "Other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant.

Samples taken as close as possible to the start of symptoms from individuals with SARS-CoV-2 viral load >1000 copies/mL were selected.

An initial analysis evaluating viral load among symptomatic cases did not indicate any differences between placebo recipients and vaccine recipients with breakthrough infection. Further analysis of an association between viral load and number and intensity of symptoms will be reported at a later date.

Statistical Analysis Methods

Population Analysis Sets
The full analysis set (FAS) included all randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment. Analysis of safety was performed on the FAS. Vaccine efficacy analyses were repeated using the FAS.

The safety subset was a subset of the FAS for analysis of solicited and unsolicited AEs.

The per-protocol (PP) efficacy population included participants in the FAS who received study vaccine, were seronegative at the time of vaccination, and had no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine. If serostatus was missing, the subject was assumed to be seronegative. If the subject had a PCR-positive result at baseline, then the subject was excluded from the per-protocol set. The primary analysis of vaccine efficacy was based on the PP population. The PP was the main analysis population for efficacy analyses. The PP population was selected as the main population for efficacy analysis to provide an assessment of vaccine efficacy in individuals without current or previous SARS-CoV-2 infection and who had no protocol deviations likely to impact vaccine efficacy. The reasons for exclusion are shown in Supplementary Figure S1. It should be noted that our population did include participants with comorbidities known to be associated with development of severe Covid-19 illness. Participants who received another vaccine prior to unblinding were included in the PP population; however, they were censored at the time of administration of the other vaccine. Participants were also censored at the time of unblinding or at the time at which they had a major protocol deviation impacting efficacy.

The reasons for excluding participants from the per-protocol analysis were mainly baseline seropositivity (9.8%). Additional reasons were reported for less than 1.5% of participants. Exclusions were balanced between randomized groups (Figure S1). Therefore, the evaluation of the co-primary endpoints in baseline seronegative participants was not expected to be impacted by the choice of the per-protocol set over the full analysis set.

Sample Size Calculation
The study target number of events (TNE) was determined using the following assumptions: (1) vaccine efficacy (VE) for molecularly confirmed, moderate to severe–critical SARS-CoV-2 infection of 60%; (2) approximately 90% power to reject a null hypothesis of H_0: VE ≤30%; (3) type 1 error rate α=2.5% to evaluate VE of the vaccine regimen (employing the sequential probability ratio test to perform a fully sequential design analysis); (4) randomization ratio of 1:1 for active versus placebo.

Under these assumptions, the total TNE to compare the active vaccine versus placebo equaled 154.

For SAEs, based on a total sample size of approximately 40,000 participants, the observation of 0 events was associated with a 2-sided 95% upper limit for the true event rate being <0.015%.

Hypothesis Testing
For hypothesis testing of primary and secondary objectives, the family-wise error rate was controlled at 2.5%. Adjustment for interim testing was done via truncated sequential probability ratio test for the co-primary endpoints. The evaluation of secondary endpoints was adjusted for multiple testing of multiple endpoints using a graphical approach according to the method of Bretz et al 2009[2] and potential stopping at an interim analysis evaluation through a Pocock boundary using Wang-Tsiatis with Delta=0.5. The timepoint and order of evaluation of multiple endpoints was done according to the graphical method detailed in the Statistical Analysis Plan. Endpoints that were evaluated inferentially at the primary analysis were summarized descriptively with 95% CI during the final analysis. All other endpoints described in the protocol, which were not part of the pre-specified hypothesis testing are summarized with descriptive 95% confidence intervals and/or *P* values without further adjustment for multiple testing. Endpoints not described in the protocol or SAP were designated as post hoc analyses.

A successful primary efficacy conclusion required:

1. Establishing the hypothesis H_1: VE>30% for each co-primary endpoint with a VE point estimate ≥50%. The study was designed to test the co-primary hypotheses of VE in the PP population. For both co-primary endpoints the following hypothesis was tested: H_0: VE ≤30% vs. H_1: VE >30% and each hypothesis was evaluated at a 2.5% one-sided significance level.

   AND

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

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

The method of Gilbert et al.[3] was used to evaluate VE over time based on the ratio of the smoothed instantaneous hazard in the vaccine and the placebo arm. More specifically, graphs were created with [(1 minus ratio (vaccine/placebo) of smoothed instantaneous hazard by time t) ×100%] and accompanying pointwise and simultaneous $(1 - \alpha) \times 100\%$ CIs over time since vaccination.

Timing of Evaluation of Co-primary Objectives

The interim monitoring for the primary analysis started as soon as the following conditions were met:

1. A minimum of 6 Covid-19 primary endpoint cases for the ≥60 years age group with onset at least 28 days after vaccination
2. At least 42 cases meeting the primary endpoint definition of moderate to severe–critical Covid-19 with onset at least 28 days after vaccination
3. A subset of at least 5 cases meeting the definition of severe–critical Covid-19 with onset at least 28 days after vaccination

Interim evaluation was performed when those conditions were fulfilled. The co-primary endpoints were met at the time of the primary analysis; thus, we proceeded with testing of secondary endpoints.

The primary analysis was supplemented with subgroup analyses for age group (18 to <60 years, ≥60 years) and presence of comorbidities (yes/no) employing a descriptive summary including (unadjusted) 95% confidence intervals to describe the VE in each subpopulation using the same methods. The ≥60 years subgroup was further subcategorized (≥70 years, ≥80 years). Safety and efficacy analyses were further summarized descriptively for subgroups (sex, race, ethnicity, age categories, country, region, presence of baseline comorbidity, baseline seropositivity status, frailty index, baseline PCR+ test, baseline VNA Ad26 status [responder/nonresponder]) and variants known to circulate to date of the finalization of the Statistical Analysis Plan. No hypothesis testing was performed in these subgroups.

The post hoc endpoints and/or subgroups analyses were:

- Short versus long Covid-19: to further describe the effect on the duration of Covid-19 based on unmet need/public health question that arose during conduct of the analysis
- Baseline SARS-CoV-2 positive Ad26 versus baseline seronegative placebo; baseline SARS-CoV-2 negative versus positive in placebo
- Covid-19 episodes requiring medical intervention linked to objective findings summaries for each severity separately

Missing Values

Follow-up time in the double blind phase was defined as the time since vaccination until the date of unblinding, study discontinuation or the last available timepoint (whichever occurred first). Missing values for baseline serology were assumed negative. Missing values for covariates were not imputed. The results were tabulated separately for the subgroup with missing covariate data.

For the SIC questionnaire, total scores were calculated based on the severity ratings for all symptoms completed by the participant per day and in cases where more than 75% of the items needed to calculate the score was not collected, then the value for that score was set to missing.

SUPPLEMENTARY RESULTS

Supplementary Efficacy Results

Symptom severity
Ad26.COV2.S recipients, compared with placebo recipients, reported lower symptom severity (**Fig. S7**) and lower viral loads in nasal swabs (0.25-0.5 log; **Fig. S8**) during the first 14 days of infection. Overall, fewer cases of Covid-19 lasting >28 days were observed for vaccine versus placebo recipients, for both moderate to severe–critical (40.5% [172/425] vs. 48.2% [419/869]) and severe–critical illness (43.2% [19/44] vs. 61.3% [106/173]) **(Fig. S9**).

Infections and asymptomatic infections
Vaccine efficacy (adjusted 95% CI) against all infections, including asymptomatic, was 41.7% (36.3–46.7) (**Table 1**); by country, efficacy (95% CI) against infection ranged from 15.7% (-84.3-61.9) to 63.6% (56.4-69.7) (**Fig. S10**). Overall efficacy (adjusted 95% CI) against asymptomatic infection was 28.9% (20.0-36.8); efficacy (95% CI) ranged from -50.7% (-255.9-33.4) to 58.8% (44.7-69.5) when evaluated by country (**Fig. S10**).

Subgroup analyses
Descriptive subgroup analyses indicated generally consistent vaccine efficacy (95% CI) against moderate to severe–critical Covid-19 ≥28 days: 46.6% (30.7-59.0) in participants ≥60 years, 54.3% (48.0-60.0) for 18-59 years, and 49.5% (38.8-58.4) and 54.7% (47.6-61.0) in participants with or without comorbidities, respectively (**Fig. S11**). Observed efficacy (95% CI) for HIV-seropositive participants was low (vaccine, 11 cases; placebo, 15 cases; efficacy 23.5% [-78.3-68.2]). No observed differences were noted between White and Black populations; however, lower point estimates of vaccine efficacy (95% CI) were observed for American Indian (including Indigenous South American)/Alaskan Native (46.5% [31.3-58.6]), Hispanic (46.6% [38.6-53.6]), and Asian (26.1% [-86.7-71.4]) populations (post hoc analysis; **Table S6**). Vaccine efficacy (95% CI) against moderate to severe–critical disease varied by country: Peru (33.1 [6.31-52.5]), Brazil (45.3 [29.1-58.0]), South Africa (49.3 [26.9-65.3]), United States (69.7 [60.7-76.9]) (**Fig. S11**). Vaccine efficacy (95% CI) by country against severe–critical Covid-19 was maintained, ranging from 61.3% (2.8-86.3) to 83.7% (-34.4-99.7) (**Fig. S12**).

Supplementary Safety Results

During the risk window of 28 days, imbalances were seen at the time of the primary analysis for tinnitus (vaccine group, n=9 vs. placebo group, n=0), urticaria (n=8 vs. n=3), convulsion (n=4 vs. n=0), and deep vein thrombosis (n=4 vs. n=2; 1 case in the vaccine group occurred in a participant with Covid-19); no imbalance was seen for pulmonary embolism (n=2 vs. n=2; 1 case in the placebo group occurred in a participant with Covid-19) (**Table S10**).

SUPPLEMENTARY FIGURES

Figure S1. Participant Disposition

Data cutoff for analysis was 9 July 2021. The full analysis set included all randomized participants who received study vaccine or placebo. The per-protocol set comprised participants who received study vaccine and had no protocol deviations likely to impact vaccine efficacy; those who were PCR positive or seropositive at the time of vaccination were excluded.

Figure S2. Cumulative Incidence of Moderate to Severe–Critical Covid-19 with Onset at Least 1 Day after Vaccination for Sequences with Substitutions Not Resulting in another SARS-CoV-2 Lineage or Variant (A), the Reference Strain (B), the Beta Variant (C), and the Alpha Variant (D) (Per-Protocol Set).

Shading indicates 95% CI. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval.

A

Participants at risk

Ad26 5e 10 vp	19577	19367	18545	17399	15740	13141	8735	5618	4447	3221	1194	207	18	6	0
Placebo	19608	19284	18222	16890	15098	12367	8044	5080	4025	2979	1098	199	19	8	0

Number of cases

Ad26 5e 10 vp	0	34	62	77	93	102	103	108	108	108	108	108	108	108	108
Placebo	0	63	145	217	263	280	291	301	305	306	307	307	307	307	307

B

Participants at risk

Ad26 5e 10 vp	19577	19367	18545	17399	15740	13141	8735	5618	4447	3221	1194	207	18	6	0
Placebo	19608	19284	18222	16890	15098	12367	8044	5080	4025	2979	1098	199	19	8	0

Number of cases

Ad26 5e 10 vp	0	16	25	42	47	47	48	48	48	48	48	48	48	48	48
Placebo	0	47	90	111	125	133	133	133	133	133	133	133	133	133	133

C

Participants at risk

Ad26 5e 10 vp	19577	19367	18545	17399	15740	13141	8735	5618	4447	3221	1194	207	18	6	0
Placebo	19608	19284	18222	16890	15098	12367	8044	5080	4025	2979	1098	199	19	8	0

Number of cases

Ad26 5e 10 vp	0	9	29	35	36	37	37	38	39	41	42	42	42	42	42
Placebo	0	8	41	54	55	56	56	58	61	61	63	63	63	63	63

D

Participants at risk

Ad26 5e 10 vp	19577	19367	18545	17399	15740	13141	8735	5618	4447	3221	1194	207	18	6	0
Placebo	19608	19284	18222	16890	15098	12367	8044	5080	4025	2979	1098	199	19	8	0

Number of cases

Ad26 5e 10 vp	0	0	0	0	0	2	3	4	7	9	9	9	9	9	9
Placebo	0	0	0	0	5	11	20	23	27	27	28	29	29	29	29

Figure S3. Vaccine Efficacy against Moderate to Severe–Critical Covid-19 with Onset at Least 14 Days (A) and with Onset at Least 28 Days after Vaccination (B) by SARS-CoV-2 Lineage (Per-Protocol Set; Additional analysis performed after the end of the double-blind period).

Confidence interval endpoints have not been adjusted for multiplicity and should not be used to infer statistical significance. [a]The risk set excludes participants who had a Covid-19 case with onset before day 15 (panel A) or before day 29 (panel B). [b]Moderate to Severe/Critical Covid-19 cases. Sequences categorized as "Other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles, CI, confidence interval; PP, per-protocol; PY, patient-year; VE, vaccine efficacy.

A

Forest Plot
Ad26 5e10 vp
Placebo
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19400) (19393)
Primary endpoint[b]
All participants 484 (19400) 6685.60 1067 (19393) 6437.60 56.3% (51.32; 60.85)
Reference strain 32 (19400) 6685.60 109 (19393) 6437.60 71.7% (57.74; 81.56)
Variant substitution 269 (19400) 6685.60 465 (19393) 6437.60 44.3% (35.13; 52.24)
B.1.1.7 (Alpha) 9 (19400) 6685.60 29 (19393) 6437.60 70.1% (35.16; 87.56)
B.1.351 (Beta) 36 (19400) 6685.60 56 (19393) 6437.60 38.1% (4.24; 60.44)
B.1.617.2/AY.1/AY.2 (Delta) 11 (19400) 6685.60 11 (19393) 6437.60 3.7% (-144.91; 62.14)
B.1.427/429 (Epsilon) 8 (19400) 6685.60 17 (19393) 6437.60 54.7% (-10.79; 83.07)
B.1.525 (Eta) 0 (19400) 6685.60 0 (19393) 6437.60
P.1 (Gamma) 76 (19400) 6685.60 115 (19393) 6437.60 36.4% (14.24; 53.01)
B.1.526 (Iota) 0 (19400) 6685.60 4 (19393) 6437.60
B.1.617.1 (Kappa) 0 (19400) 6685.60 0 (19393) 6437.60
C.37 (Lambda) 45 (19400) 6685.60 50 (19393) 6437.60 13.3% (-32.30; 43.38)
P.3 (Theta) 0 (19400) 6685.60 0 (19393) 6437.60
P.2 (Zeta) 34 (19400) 6685.60 93 (19393) 6437.60 64.8% (47.34; 76.96)
B.1.621 38 (19400) 6685.60 58 (19393) 6437.60 36.9% (3.39; 59.23)
C.36.3 0 (19400) 6685.60 0 (19393) 6437.60
R.1 1 (19400) 6685.60 0 (19393) 6437.60
B.1.1.519 2 (19400) 6685.60 6 (19393) 6437.60 67.9% (-79.50; 96.83)
Other+E484K 9 (19400) 6685.60 26 (19393) 6437.60 66.7% (26.60; 86.26)
Other 78 (19400) 6685.60 280 (19393) 6437.60 73.2% (65.41; 79.40)
No sequencing data available 105 (19400) 6685.60 213 (19393) 6437.60 52.5% (39.76; 62.79)
-100
0
100
VE% (95% CI)

B

Ad26 5e10 vp
Placebo
Forest Plot
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19113) (18916)
Primary endpoint[b]
All participants 433 (19113) 6658.36 883 (18916) 6396.14 52.9% (47.09; 58.11)
Reference strain 30 (19113) 6658.36 71 (18916) 6396.14 59.4% (36.98; 74.43)
Variant substitution 243 (19113) 6658.36 423 (18916) 6396.14 44.8% (35.23; 53.07)
B.1.1.7 (Alpha) 9 (19113) 6658.36 29 (18916) 6396.14 70.2% (35.31; 87.59)
B.1.351 (Beta) 23 (19113) 6658.36 46 (18916) 6396.14 52.0% (19.11; 72.21)
B.1.617.2/AY.1/AY.2 (Delta) 11 (19113) 6658.36 11 (18916) 6396.14 3.9% (-144.33; 62.23)
B.1.427/429 (Epsilon) 5 (19113) 6658.36 14 (18916) 6396.14 65.7% (-0.80; 90.33)
B.1.525 (Eta) 0 (19113) 6658.36 0 (18916) 6396.14
P.1 (Gamma) 76 (19113) 6658.36 115 (18916) 6396.14 36.5% (14.44; 53.12)
B.1.526 (Iota) 0 (19113) 6658.36 4 (18916) 6396.14
B.1.617.1 (Kappa) 0 (19113) 6658.36 0 (18916) 6396.14
C.37 (Lambda) 45 (19113) 6658.36 50 (18916) 6396.14 13.5% (-31.99; 43.51)
P.3 (Theta) 0 (19113) 6658.36 0 (18916) 6396.14
P.2 (Zeta) 25 (19113) 6658.36 67 (18916) 6396.14 64.2% (42.49; 78.31)
B.1.621 38 (19113) 6658.36 58 (18916) 6396.14 37.1% (3.62; 59.33)
C.36.3 0 (19113) 6658.36 0 (18916) 6396.14
R.1 1 (19113) 6658.36 0 (18916) 6396.14
B.1.1.519 2 (19113) 6658.36 5 (18916) 6396.14 61.6% (-134.71; 96.34)
Other+E484K 8 (19113) 6658.36 24 (18916) 6396.14 68.0% (26.33; 87.56)
Other 68 (19113) 6658.36 211 (18916) 6396.14 69.0% (59.13; 76.80)
No sequencing data available 92 (19113) 6658.36 178 (18916) 6396.14 50.4% (35.79; 61.83)
-100
0
100
VE% (95% CI)

Figure S4. Summary of Vaccine Efficacy Against First Occurrence of Severe–Critical Covid-19 with Onset at Least 14 Days (A) and with Onset at Least 28 Days after Vaccination (B) by SARS-CoV-2 Lineage (Per-Protocol Set).

Confidence interval endpoints have not been adjusted for multiplicity and should not be used to infer statistical significance. [a]The risk set excludes participants who had a Covid-19 case with onset before day 15 (panel A) or before day 29 (panel B). Sequences categorized as "Other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval; PP, per-protocol; PY, patient-year; VE, vaccine efficacy.

A

Ad26 5e10 vp
Placebo
Forest Plot
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19400) (19398)
Severe/critical Covid-19 cases
All participants 56 (19400) 6774.58 205 (19398) 6625.15 73.3% (63.94; 80.49)
Reference strain 2 (19400) 6774.58 19 (19398) 6625.15 89.7% (57.33; 98.84)
Variant substitution 31 (19400) 6774.58 101 (19398) 6625.15 70.0% (54.72; 80.61)
B.1.1.7 (Alpha) 2 (19400) 6774.58 4 (19398) 6625.15 51.1% (-241.18; 95.58)
B.1.351 (Beta) 7 (19400) 6774.58 23 (19398) 6625.15 70.2% (28.35; 89.21)
B.1.617.2/AY.1/AY.2 (Delta) 2 (19400) 6774.58 2 (19398) 6625.15
B.1.427/429 (Epsilon) 2 (19400) 6774.58 2 (19398) 6625.15
B.1.525 (Eta) 0 (19400) 6774.58 0 (19398) 6625.15
P.1 (Gamma) 9 (19400) 6774.58 24 (19398) 6625.15 63.3% (18.28; 85.00)
B.1.526 (Iota) 0 (19400) 6774.58 1 (19398) 6625.15
B.1.617.1 (Kappa) 0 (19400) 6774.58 0 (19398) 6625.15
C.37 (Lambda) 3 (19400) 6774.58 9 (19398) 6625.15 67.4% (-30.62; 94.32)
P.3 (Theta) 0 (19400) 6774.58 0 (19398) 6625.15
P.2 (Zeta) 1 (19400) 6774.58 11 (19398) 6625.15 91.1% (38.83; 99.79)
B.1.621 4 (19400) 6774.58 19 (19398) 6625.15 79.4% (38.05; 94.91)
C.36.3 0 (19400) 6774.58 0 (19398) 6625.15
R.1 0 (19400) 6774.58 0 (19398) 6625.15
B.1.1.519 0 (19400) 6774.58 0 (19398) 6625.15
Other+E484K 1 (19400) 6774.58 6 (19398) 6625.15 83.7% (-34.34; 99.65)
Other 8 (19400) 6774.58 42 (19398) 6625.15 81.4% (59.84; 92.45)
No sequencing data available 15 (19400) 6774.58 43 (19398) 6625.15 65.9% (37.36; 82.40)
-100
0
100
VE% (95% CI)

B

Ad26 5e10 vp
Placebo
Forest Plot
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19113) (18924)
Severe/critical Covid-19 cases
All participants 46 (19113) 6733.82 176 (18924) 6542.13 74.6% (64.70; 82.06)
Reference strain 1 (19113) 6733.82 14 (18924) 6542.13 93.1% (54.39; 99.84)
Variant substitution 27 (19113) 6733.82 93 (18924) 6542.13 71.8% (56.31; 82.34)
B.1.1.7 (Alpha) 2 (19113) 6733.82 4 (18924) 6542.13 51.4% (-238.95; 95.61)
B.1.351 (Beta) 4 (19113) 6733.82 18 (18924) 6542.13 78.4% (34.46; 94.69)
B.1.617.2/AY.1/AY.2 (Delta) 2 (19113) 6733.82 2 (18924) 6542.13
B.1.427/429 (Epsilon) 1 (19113) 6733.82 2 (18924) 6542.13
B.1.525 (Eta) 0 (19113) 6733.82 0 (18924) 6542.13
P.1 (Gamma) 9 (19113) 6733.82 24 (18924) 6542.13 63.6% (18.81; 85.10)
B.1.526 (Iota) 0 (19113) 6733.82 1 (18924) 6542.13
B.1.617.1 (Kappa) 0 (19113) 6733.82 0 (18924) 6542.13
C.37 (Lambda) 3 (19113) 6733.82 9 (18924) 6542.13 67.6% (-29.77; 94.36)
P.3 (Theta) 0 (19113) 6733.82 0 (18924) 6542.13
P.2 (Zeta) 1 (19113) 6733.82 8 (18924) 6542.13 87.9% (9.42; 99.73)
B.1.621 4 (19113) 6733.82 19 (18924) 6542.13 79.5% (38.45; 94.94)
C.36.3 0 (19113) 6733.82 0 (18924) 6542.13
R.1 0 (19113) 6733.82 0 (18924) 6542.13
B.1.1.519 0 (19113) 6733.82 0 (18924) 6542.13
Other+E484K 1 (19113) 6733.82 6 (18924) 6542.13 83.8% (-33.46; 99.65)
Other 8 (19113) 6733.82 32 (18924) 6542.13 75.7% (46.18; 90.33)
No sequencing data available 10 (19113) 6733.82 37 (18924) 6542.13 73.7% (46.14; 88.36)
-100
0
100
VE% (95% CI)

Figure S5. Cumulative Incidence of Medical Intervention Over Time (A) and Vaccine Efficacy Over Time for Severe–Critical Cases Requiring Medical Intervention (B) (Per-Protocol Set; Post-Hoc Analysis).

Analysis was conducted in a subset of the of the protocol-specified population. Shading indicates 95% CI. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval.

A

Participants at risk

Ad26 5e 10 vp	19726	19629	18961	17988	16440	13881	9346	6080	4822	3510	1363	248	22	6	0
Placebo	19787	19665	18911	17894	16305	13645	9117	5901	4692	3524	1389	267	23	10	0

Number of cases

Ad26 5e 10 vp	0	6	7	8	10	11	14	20	21	23	23	23	23	23	23
Placebo	0	9	20	37	49	58	67	75	80	80	81	83	83	83	83

B

Numbers at risk

Placebo	19589	19169	17595	15291	9897	5115	3860	1293
Ad26 5e10 vp	19562	19241	17786	15617	10310	5447	4061	1318

Figure S6. Vaccine Efficacy Against First Occurrence of Molecularly Confirmed Covid-19 Requiring Medical Intervention with Onset at Least 14 Days (A) and with Onset at Least 28 Days after Vaccination (B) by SARS-CoV-2 Lineage (Per-Protocol Set).

95% CIs for vaccine efficacy against Covid-19 requiring medical intervention are adjusted for multiplicity based on pre-specified procedures for family-wise type I error control. Except as indicated by **, all others were descriptive 95% CI, no adjustments for multiple testing were made. **indicates adjusted CI. [a]The risk set excludes participants who had a Covid-19 case with an onset before day 15 (panel A) or day 29 (panel B). Sequences categorized as "Other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval; PP, per-protocol; PY, patient-year; VE, vaccine efficacy.

A

Ad26 5e10 vp
Placebo
Forest Plot
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19400) (19398)
Req. Medical Intervention
All participants** 18 (19400) 6783.90 74 (19398) 6656.73 76.1% (56.86; 87.67)
Reference strain 0 (19400) 6783.90 4 (19398) 6656.73
Variant substitution 11 (19400) 6783.90 36 (19398) 6656.73 70.0% (39.79; 86.23)
B.1.1.7 (Alpha) 1 (19400) 6783.90 1 (19398) 6656.73
B.1.351 (Beta) 0 (19400) 6783.90 7 (19398) 6656.73 100.0% (31.92; 100.00)
B.1.617.2/AY.1/AY.2 (Delta) 0 (19400) 6783.90 0 (19398) 6656.73
B.1.427/429 (Epsilon) 0 (19400) 6783.90 0 (19398) 6656.73
B.1.525 (Eta) 0 (19400) 6783.90 0 (19398) 6656.73
P.1 (Gamma) 4 (19400) 6783.90 15 (19398) 6656.73 73.8% (17.86; 93.68)
B.1.526 (Iota) 0 (19400) 6783.90 0 (19398) 6656.73
B.1.617.1 (Kappa) 0 (19400) 6783.90 0 (19398) 6656.73
C.37 (Lambda) 5 (19400) 6783.90 6 (19398) 6656.73 18.2% (-221.58; 80.26)
P.3 (Theta) 0 (19400) 6783.90 0 (19398) 6656.73
P.2 (Zeta) 0 (19400) 6783.90 1 (19398) 6656.73
B.1.621 1 (19400) 6783.90 4 (19398) 6656.73
C.36.3 0 (19400) 6783.90 0 (19398) 6656.73
R.1 0 (19400) 6783.90 0 (19398) 6656.73
B.1.1.519 0 (19400) 6783.90 0 (19398) 6656.73
Other+E484K 0 (19400) 6783.90 2 (19398) 6656.73
Other 1 (19400) 6783.90 16 (19398) 6656.73 93.9% (60.52; 99.85)
No sequencing data available 6 (19400) 6783.90 18 (19398) 6656.73 67.3% (13.99; 89.37)
-100
0
100
VE% (95% CI)

B

Ad26 5e10 vp
Placebo
Forest Plot
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19113) (18924)
Req. Medical Intervention
All participants** 16 (19113) 6739.75 64 (18924) 6567.09 75.6% (54.26; 88.00)
Reference strain 0 (19113) 6739.75 3 (18924) 6567.09
Variant substitution 11 (19113) 6739.75 33 (18924) 6567.09 67.5% (34.12; 85.19)
B.1.1.7 (Alpha) 1 (19113) 6739.75 1 (18924) 6567.09
B.1.351 (Beta) 0 (19113) 6739.75 5 (18924) 6567.09
B.1.617.2/AY.1/AY.2 (Delta) 0 (19113) 6739.75 0 (18924) 6567.09
B.1.427/429 (Epsilon) 0 (19113) 6739.75 0 (18924) 6567.09
B.1.525 (Eta) 0 (19113) 6739.75 0 (18924) 6567.09
P.1 (Gamma) 4 (19113) 6739.75 15 (18924) 6567.09 74.0% (18.44; 93.72)
B.1.526 (Iota) 0 (19113) 6739.75 0 (18924) 6567.09
B.1.617.1 (Kappa) 0 (19113) 6739.75 0 (18924) 6567.09
C.37 (Lambda) 5 (19113) 6739.75 6 (18924) 6567.09 18.8% (-219.33; 80.40)
P.3 (Theta) 0 (19113) 6739.75 0 (18924) 6567.09
P.2 (Zeta) 0 (19113) 6739.75 0 (18924) 6567.09
B.1.621 1 (19113) 6739.75 4 (18924) 6567.09
C.36.3 0 (19113) 6739.75 0 (18924) 6567.09
R.1 0 (19113) 6739.75 0 (18924) 6567.09
B.1.1.519 0 (19113) 6739.75 0 (18924) 6567.09
Other+E484K 0 (19113) 6739.75 2 (18924) 6567.09
Other 1 (19113) 6739.75 12 (18924) 6567.09 91.9% (45.12; 99.81)
No sequencing data available 4 (19113) 6739.75 16 (18924) 6567.09 75.6% (24.49; 94.07)
-100
0
100
VE% (95% CI)

Figure S7. Mean SE Plot of the Total Symptoms of Infection Score of Symptomatic Covid-19 Cases with Onset at Least 14 Days after Vaccination Over Time for Confirmed Cases (A), with Onset at Least 28 Days after Vaccination (B), and Confirmed Severe Cases at Least 14 Days after Vaccination (C), and at Least 28 Days after Vaccination (D) (Per-Protocol Set).

In part A, the graph is truncated at Day 49. SE, standard error; vp, viral particles.

A

B

Confirmed cases
Ad26.COV2.S 5x10^10 vp
Placebo
Ad26.COV2.S 5x10^10 vp
Placebo
Average symptom score
mean ± SE
Time
Number of Patients
Ad26.COV2.S 5x10^10 vp 300 331 347 314 254 196 133 84 67 45 29 25 15 11 7
Placebo 569 661 681 627 541 448 328 238 179 120 86 60 43 33 23

C

Confirmed Cases - Severe
Ad26.COV2.S 5x10^10 vp
Placebo
Ad26.COV2.S 5x10^10 vp
Placebo
Average symptom score
mean ± SE
Time
Number of Patients
Ad26.COV2.S 5x10^10 vp 36 30 19 9 3
Placebo 118 127 94 49 22 8 2 2 1 1

D

Confirmed Cases - Severe
Ad26.COV2.S 5x10^10 vp
Placebo
Ad26.COV2.S 5x10^10 vp
Placebo
Average symptom score
mean ± SE
2.5
2.0
1.5
1.0
0.5
0.0
1
10
20
30
40
50
60
70
80
90
Time
Number of Patients
Ad26.COV2.S 5x10^10 vp 31 25 13 7 3
Placebo 106 108 82 38 18 7 2 2 1 1

Figure S8. Viral Load For Symptomatic Covid-19 Cases with Onset At Least 14 Days after Vaccination (A) and at Least 28 Days after Vaccination (B), and Viral Load and Symptom Scores for Cases with Onset at Least 14 Days after Vaccination for Constitutional Symptoms (C), Gastrointestinal Symptoms (D), and Lower Respiratory Symptoms (E) (Per-Protocol Set)

vp, viral particles.

A

B

Number of Patients

Ad26.COV2.S 5x10^10 vp	261	363	372	311	289	225	160	108	79	58	42	31	23	18	12	7	6	4	2						
Placebo	489	683	718	635	576	464	369	238	177	132	89	57	47	35	26	14	6	7	6	4	1	2	1	2	8

C

Number of Subjects

Ad26	256	369	368	305	282	214	143	104	64	51	38	26	18	14	7	6	3	1	1						2
Placebo	520	768	794	688	606	489	365	244	180	135	86	58	41	30	23	11	7	5	4	2					7

D

Number of Subjects

Ad26	256	369	368	305	282	214	143	104	64	51	38	26	18	14	7	6	3	1	1					2
Placebo	520	768	794	688	606	489	365	244	180	135	86	58	41	30	23	11	7	5	4	2				7

E

Number of Subjects

Ad26	256	369	368	305	282	214	143	104	64	51	38	26	18	14	7	6	3	1	1					2
Placebo	520	768	794	688	606	489	365	244	180	135	86	58	41	30	23	11	7	5	4	2				7

Figure S9. Cases of Moderate to Severe–Critical (A) and Severe–Critical Covid-19 (B) with Onset at Least 28 Days after Vaccination by Covid-19 Duration (Post-Hoc Analysis).

Long Covid-19 was defined as lasting >28 days. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; vp, viral particles.

A

B

Overall
200
180
160
140
120
100
80
60
40
20
0
Number of cases
38.7%
61.3%
56.8%
43.2%
Ad26 5e10 vp
Placebo
Ad26 5e10 vp-Placebo
Group:
Long COVID-19
Short COVID-19

Figure S10. Vaccine Efficacy Against Any Infection (A) and Against Any Asymptomatic Infection (B) with Onset at Least 28 Days after Vaccination, by Country.

95% CIs for vaccine efficacy against any Covid-19 infection and against asymptomatic infections are adjusted for multiplicity based on pre-specified procedures for family-wise type I error control. **indicates adjusted CI. [a]The risk set excludes participants who had a Covid-19 case with an onset before day 29. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval; PP, per-protocol; PY, patient-year; VE, vaccine efficacy.

A

B

Ad26 5e10 vp
Placebo
Forest Plot
#Cases(N) PY #Cases(N) PY VE% (95% CI)
Analysis set: PP (19577) (19608)
Risk set[a] (19113) (18924)
Asymptomatic infections
All participants** 498 (19113) 6581.00 669 (18924) 6289.27 28.9% (19.99;36.78)
By Country
Argentina 20 (1393) 553.95 24 (1398) 533.11 19.8% (-51.50;57.98)
Brazil 42 (3339) 979.34 48 (3291) 950.72 15.1% (-31.27;45.22)
Chile 7 (527) 147.43 5 (533) 142.48 -35.3% (-440.61;63.04)
Colombia 55 (1829) 779.51 60 (1823) 747.84 12.1% (-28.96;40.13)
Mexico 5 (206) 101.56 10 (216) 100.34 50.6% (-58.64;86.75)
Peru 17 (568) 275.90 11 (570) 269.03 -50.7% (-255.94;33.41)
United States 67 (8829) 2578.85 152 (8663) 2412.42 58.8% (44.69;69.54)
South Africa 285 (2422) 1164.46 359 (2430) 1133.32 22.7% (9.48;34.10)
-100
0
100
VE% (95% CI)

Figure S11. Vaccine Efficacy Against Moderate to Severe–Critical Covid-19 by Subgroups for Cases with Onset at Least 14 Days (A) and with Onset at Least 28 Days after Vaccination (B) (Per-Protocol Set, Seronegative at Baseline, Confirmed Cases).

Confidence interval endpoints have not been adjusted for multiplicity and should not be used to infer statistical significance. [a]The risk set excludes participants who had a Covid-19 case with onset before day 15 (panel A) or before day 29 (panel B). [b]Moderate to Severe/Critical Covid-19 cases. Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval; PP, per-protocol; PY, patient-year; VE, vaccine efficacy.

A

	Ad26 5e10 vp		Placebo		
Forest Plot	#Cases(N)	PY	#Cases(N)	PY	VE% (95% CI)
Analysis set: PP	(19577)		(19608)		
Risk set[a]	(19400)		(19398)		
Primary endpoint[b]					
All participants	484 (19400)	6685.60	1067 (19398)	6440.18	56.3% (51.30;60.84)
By Agegroup 1					
18-59 years	381 (12665)	4682.12	847 (12674)	4514.15	56.6% (51.00;61.67)
>=60 years	103 (6735)	2003.48	220 (6724)	1926.03	55.0% (42.87;64.73)
By Comorbidities					
Yes	189 (7959)	2618.28	402 (7980)	2529.58	54.6% (45.87;61.99)
No	295 (11441)	4067.32	665 (11418)	3910.60	57.3% (51.01;62.94)
By Country					
Argentina	45 (1397)	556.46	102 (1408)	536.30	57.5% (39.05;70.75)
Brazil	109 (3358)	983.41	212 (3345)	958.87	49.9% (36.55;60.58)
Chile	6 (527)	147.93	9 (536)	142.84	35.6% (-102.51;81.15)
Colombia	105 (1837)	786.49	209 (1848)	758.14	51.6% (38.49;62.06)
Mexico	3 (207)	101.68	9 (218)	100.60	67.0% (-32.15;94.26)
Peru	61 (569)	278.54	93 (574)	271.73	36.0% (10.67;54.45)
United States	93 (9057)	2604.68	323 (9002)	2453.69	72.9% (65.74;78.70)
South Africa	62 (2448)	1226.38	110 (2467)	1218.01	44.0% (22.89;59.67)
By Age and comorbidities 1					
18-59, no	253 (8185)	3074.64	568 (8231)	2971.27	57.0% (49.99;63.03)
18-59, yes	128 (4480)	1607.47	279 (4443)	1542.87	56.0% (45.53;64.56)
>=60, no	42 (3256)	992.68	97 (3187)	939.32	59.0% (40.58;72.18)
>=60, yes	61 (3479)	1010.80	123 (3537)	986.71	51.6% (33.67;64.98)
By HIV infection					
Yes	13 (460)	189.03	16 (494)	196.62	15.5% (-87.39;62.60)
No HIV	471 (18940)	6496.57	1051 (18904)	6243.56	56.9% (51.94;61.45)
By Sex					
Male	267 (10798)	3790.23	581 (10742)	3641.23	55.9% (48.88;61.95)
Female	217 (8599)	2894.45	486 (8652)	2797.57	56.8% (49.25;63.40)
Undifferentiated	0 (2)	0.62	0 (4)	1.39	
Unknown	0 (1)	0.29	0 (0)		
By Race					
Amer. Indian/Alaskan	103 (1630)	713.69	190 (1607)	667.41	49.3% (35.23;60.51)
Asian	12 (701)	192.33	17 (641)	171.33	37.1% (-39.70;72.60)
Black or African Amer.	62 (3330)	1408.66	139 (3324)	1373.46	56.5% (40.93;68.30)
Native Hawaiian/other	0 (52)	16.89	1 (42)	11.76	
White	237 (12075)	3754.79	574 (12070)	3600.10	60.4% (53.86;66.12)
Multiple	51 (1021)	408.61	110 (1070)	413.21	53.1% (34.08;67.04)
Unknown	12 (260)	83.79	17 (266)	90.87	23.4% (-70.10;66.64)
Not Reported	7 (331)	106.84	19 (378)	112.02	61.4% (4.04;86.28)
Missing	0 (0)		0 (0)		
By Ethnicity					
Hispanic/Latino	336 (8695)	3077.28	664 (8817)	2998.11	50.7% (43.70;56.89)
Not Hispanic/Latino	137 (10217)	3442.63	382 (10099)	3291.66	65.7% (58.21;72.00)
Not Reported	7 (313)	104.44	12 (326)	100.65	43.8% (-54.88;81.25)
Unknown	4 (175)	61.25	9 (156)	49.75	63.9% (-29.35;91.88)
Missing	0 (0)		0 (0)		
By Region					
Latin America	329 (7895)	2854.53	634 (7929)	2768.48	49.7% (42.41;56.08)
Northern America	93 (9057)	2604.68	323 (9002)	2453.69	72.9% (65.74;78.70)
Southern Africa	62 (2448)	1226.38	110 (2467)	1218.01	44.0% (22.89;59.67)

B

	Ad26 5e10 vp #Cases(N)	Ad26 5e10 vp PY	Placebo #Cases(N)	Placebo PY	VE% (95% CI)
Analysis set: PP	(19577)		(19608)		
Risk set[a]	(19113)		(18924)		
Primary endpoint[b]					
All participants	433 (19113)	6658.36	883 (18924)	6400.36	52.9% (47.06;58.08)
By Agegroup 1					
18-59 years	340 (12489)	4663.76	716 (12350)	4486.71	54.3% (47.95;59.97)
>=60 years	93 (6624)	1994.59	167 (6574)	1913.65	46.6% (30.74;58.99)
By Comorbidities					
Yes	165 (7815)	2604.54	315 (7763)	2511.65	49.5% (38.83;58.42)
No	268 (11298)	4053.82	568 (11161)	3888.71	54.7% (47.57;61.00)
By Country					
Argentina	45 (1393)	555.67	95 (1398)	535.50	54.4% (34.25;68.72)
Brazil	94 (3339)	981.59	167 (3291)	954.32	45.3% (29.12;57.96)
Chile	6 (527)	147.93	7 (533)	142.49	17.4% (-186.91;77.08)
Colombia	102 (1829)	784.88	189 (1823)	755.14	48.1% (33.59;59.60)
Mexico	2 (206)	101.64	7 (216)	100.48	71.8% (-48.34;97.14)
Peru	61 (568)	278.17	89 (570)	271.46	33.1% (6.31;52.52)
United States	77 (8829)	2587.01	239 (8663)	2430.10	69.7% (60.72;76.90)
South Africa	46 (2422)	1221.46	90 (2430)	1210.86	49.3% (26.94;65.28)
By Age and comorbidities 1					
18-59, no	228 (8088)	3064.82	491 (8032)	2954.18	55.2% (47.52;61.92)
18-59, yes	112 (4401)	1598.95	225 (4318)	1532.53	52.3% (39.89;62.31)
>=60, no	40 (3210)	989.00	77 (3129)	934.53	50.9% (27.17;67.37)
>=60, yes	53 (3414)	1005.59	90 (3445)	979.12	42.7% (18.61;59.95)
By HIV infection					
Yes	11 (453)	188.14	15 (488)	196.26	23.5% (-78.25;68.22)
No HIV	422 (18660)	6470.21	868 (18436)	6204.10	53.4% (47.57;58.60)
By Sex					
Male	240 (10661)	3777.47	481 (10501)	3621.40	52.2% (44.04;59.20)
Female	193 (8449)	2879.97	402 (8420)	2777.62	53.7% (44.89;61.20)
Undifferentiated	0 (2)	0.62	0 (3)	1.34	
Unknown	0 (1)	0.29	0 (0)		
By Race					
Amer. Indian/Alaskan	100 (1620)	711.31	175 (1587)	665.34	46.5% (31.28;58.62)
Asian	10 (669)	190.13	12 (607)	168.67	26.1% (-86.71;71.39)
Black or African Amer.	47 (3282)	1401.18	110 (3251)	1363.97	58.4% (40.97;71.09)
Native Hawaiian/other	0 (52)	16.89	1 (41)	11.69	
White	209 (11893)	3740.54	465 (11773)	3578.87	57.0% (49.26;63.65)
Multiple	49 (1015)	408.26	95 (1046)	410.84	48.1% (25.98;64.00)
Unknown	11 (256)	83.50	13 (257)	90.31	8.5% (-121.38;62.88)
Not Reported	7 (326)	106.55	12 (362)	110.67	39.4% (-66.91;79.79)
Missing	0 (0)		0 (0)		
By Ethnicity					
Hispanic/Latino	316 (8632)	3069.95	575 (8658)	2985.44	46.6% (38.59;53.56)
Not Hispanic/Latino	108 (10000)	3423.59	293 (9798)	3265.40	64.8% (56.02;72.07)
Not Reported	7 (311)	104.31	10 (318)	100.11	32.8% (-95.51;78.30)
Unknown	2 (170)	60.50	5 (150)	49.41	67.3% (-99.54;96.89)
Missing	0 (0)		0 (0)		
By Region					
Latin America	310 (7862)	2849.89	554 (7831)	2759.39	45.8% (37.63;53.01)
Northern America	77 (8829)	2587.01	239 (8663)	2430.10	69.7% (60.72;76.90)
Southern Africa	46 (2422)	1221.46	90 (2430)	1210.86	49.3% (26.94;65.28)

Figure S12. Vaccine Efficacy Against Severe–Critical Covid-19 By Subgroups for Cases with Onset at Least 14 Days (A) and Onset at Least 28 days after Vaccination (B) (Per-Protocol Set, Seronegative at Baseline, Confirmed Cases).

Confidence interval endpoints have not been adjusted for multiplicity and should not be used to infer statistical significance. [a]The risk set excludes participants who had a Covid-19 case with onset before day 15 (panel A) or before day 29 (panel B). Ad26 5e 10 vp, Ad26.COV2.S at 5×10^{10} viral particles; CI, confidence interval; PP, per-protocol; PY, patient-year; VE, vaccine efficacy.

A

	Ad26 5e10 vp #Cases(N)	Ad26 5e10 vp PY	Placebo #Cases(N)	Placebo PY	VE% (95% CI)
Analysis set: PP	(19577)		(19608)		
Risk set[a]	(19400)		(19398)		
Severe/critical cases					
All participants	56 (19400)	6774.58	205 (19398)	6625.15	73.3% (63.94;80.49)
By Agegroup 1					
18-59 years	39 (12665)	4755.48	145 (12674)	4668.43	73.6% (62.17;81.95)
>=60 years	17 (6735)	2019.10	60 (6724)	1956.72	72.5% (52.31;84.98)
By Comorbidities					
Yes	28 (7959)	2652.53	100 (7980)	2594.01	72.6% (58.01;82.67)
No	28 (11441)	4122.05	105 (11418)	4031.13	73.9% (60.12;83.46)
By Country					
Argentina	1 (1397)	563.89	7 (1408)	553.70	86.0% (-9.19;99.69)
Brazil	6 (3358)	999.73	31 (3345)	991.73	80.8% (53.29;93.45)
Chile	0 (527)	149.23	0 (536)	144.43	
Colombia	17 (1837)	804.51	71 (1848)	788.70	76.5% (59.73;87.04)
Mexico	2 (207)	102.03	3 (218)	102.47	
Peru	7 (569)	293.97	19 (574)	293.92	63.2% (8.49;86.91)
United States	11 (9057)	2620.21	34 (9002)	2511.92	69.0% (37.31;85.82)
South Africa	12 (2448)	1241.01	40 (2467)	1238.28	70.1% (41.80;85.70)
By Age and comorbidities 1					
18-59, no	27 (8185)	3121.84	86 (8231)	3076.59	69.1% (51.84;80.70)
18-59, yes	12 (4480)	1633.64	59 (4443)	1591.84	80.2% (62.74;90.30)
>=60, no	1 (3256)	1000.21	19 (3187)	954.55	95.0% (68.40;99.88)
>=60, yes	16 (3479)	1018.89	41 (3537)	1002.17	61.6% (30.10;79.89)
By HIV infection					
Yes	3 (460)	191.76	4 (494)	199.06	22.1% (-360.20;88.60)
No HIV	53 (18940)	6582.82	201 (18904)	6426.09	74.3% (65.01;81.35)
By Sex					
Male	34 (10798)	3837.56	110 (10742)	3741.65	69.9% (55.37;80.12)
Female	22 (8599)	2936.10	95 (8652)	2882.11	77.3% (63.56;86.39)
Undifferentiated	0 (2)	0.62	0 (4)	1.39	
Unknown	0 (1)	0.29	0 (0)		
By Race					
Amer. Indian/Alaskan	18 (1630)	734.08	58 (1607)	699.82	70.4% (49.06;83.60)
Asian	1 (701)	193.99	0 (641)	174.49	
Black or African Amer.	13 (3330)	1421.35	47 (3324)	1396.91	72.8% (48.93;86.51)
Native Hawaiian/other	0 (52)	16.89	0 (42)	11.85	
White	18 (12075)	3794.68	67 (12070)	3697.92	73.8% (55.42;85.36)
Multiple	6 (1021)	418.94	30 (1070)	432.77	79.3% (49.55;92.97)
Unknown	0 (260)	86.46	1 (266)	94.90	
Not Reported	0 (331)	108.17	2 (378)	116.47	
Missing	0 (0)		0 (0)		
By Ethnicity					
Hispanic/Latino	34 (8695)	3136.76	132 (8817)	3110.63	74.5% (62.52;83.02)
Not Hispanic/Latino	21 (10217)	3470.41	70 (10099)	3359.43	71.0% (52.13;83.07)
Not Reported	0 (313)	105.59	0 (326)	103.66	
Unknown	1 (175)	61.82	3 (156)	51.43	
Missing	0 (0)		0 (0)		
By Region					
Latin America	33 (7895)	2913.36	131 (7929)	2874.95	75.1% (63.35;83.57)
Northern America	11 (9057)	2620.21	34 (9002)	2511.92	69.0% (37.31;85.82)
Southern Africa	12 (2448)	1241.01	40 (2467)	1238.28	70.1% (41.80;85.70)

B

	Ad26 5e10 vp #Cases(N)	Ad26 5e10 vp PY	Placebo #Cases(N)	Placebo PY	VE% (95% CI)
Analysis set: PP	(19577)		(19608)		
Risk set[a]	(19113)		(18924)		
Severe/critical cases					
All participants	46 (19113)	6733.82	176 (18924)	6542.13	74.6% (64.70;82.06)
By Agegroup 1					
18-59 years	34 (12489)	4724.95	128 (12350)	4607.16	74.1% (61.94;82.80)
>=60 years	12 (6624)	2008.87	48 (6574)	1934.97	75.9% (53.98;88.36)
By Comorbidities					
Yes	22 (7815)	2632.70	80 (7763)	2557.46	73.3% (56.73;84.14)
No	24 (11298)	4101.12	96 (11161)	3984.67	75.7% (61.69;85.15)
By Country					
Argentina	1 (1393)	563.09	6 (1398)	550.85	83.7% (-34.39;99.65)
Brazil	5 (3339)	994.17	28 (3291)	977.22	82.4% (53.96;94.71)
Chile	0 (527)	149.23	0 (533)	143.70	
Colombia	17 (1829)	801.40	64 (1823)	780.69	74.1% (55.28;85.79)
Mexico	1 (206)	101.99	2 (216)	101.89	
Peru	7 (568)	293.60	18 (570)	292.53	61.3% (2.77;86.32)
United States	7 (8829)	2599.64	26 (8663)	2469.98	74.4% (39.49;90.63)
South Africa	8 (2422)	1230.69	32 (2430)	1225.26	75.1% (44.85;90.09)
By Age and comorbidities 1					
18-59, no	23 (8088)	3105.26	80 (8032)	3038.78	71.9% (54.79;83.12)
18-59, yes	11 (4401)	1619.69	48 (4318)	1568.39	77.8% (56.67;89.61)
>=60, no	1 (3210)	995.85	16 (3129)	945.90	94.1% (61.79;99.86)
>=60, yes	11 (3414)	1013.02	32 (3445)	989.07	66.4% (31.67;84.74)
By HIV infection					
Yes	3 (453)	189.90	4 (488)	198.23	21.7% (-362.79;88.53)
No HIV	43 (18660)	6543.92	172 (18436)	6343.90	75.8% (65.98;83.07)
By Sex					
Male	28 (10661)	3817.90	94 (10501)	3699.02	71.1% (55.58;81.79)
Female	18 (8449)	2915.01	82 (8420)	2841.77	78.6% (64.04;87.91)
Undifferentiated	0 (2)	0.62	0 (3)	1.34	
Unknown	0 (1)	0.29	0 (0)		
By Race					
Amer. Indian/Alaskan	18 (1620)	730.21	53 (1587)	694.12	67.7% (43.99;82.20)
Asian	0 (669)	191.52	0 (607)	170.86	
Black or African Amer.	8 (3282)	1409.52	37 (3251)	1380.69	78.8% (53.79;91.48)
Native Hawaiian/other	0 (52)	16.89	0 (41)	11.77	
White	14 (11893)	3773.89	58 (11773)	3651.49	76.6% (57.60;87.97)
Multiple	6 (1015)	418.00	25 (1046)	427.19	75.5% (38.75;91.77)
Unknown	0 (256)	85.92	1 (257)	93.32	
Not Reported	0 (326)	107.88	2 (362)	112.68	
Missing	0 (0)		0 (0)		
By Ethnicity					
Hispanic/Latino	32 (8632)	3124.23	118 (8658)	3076.53	73.3% (60.24;82.52)
Not Hispanic/Latino	14 (10000)	3443.36	56 (9798)	3313.44	75.9% (56.21;87.63)
Not Reported	0 (311)	105.46	0 (318)	102.30	
Unknown	0 (170)	60.76	2 (150)	49.86	
Missing	0 (0)		0 (0)		
By Region					
Latin America	31 (7862)	2903.49	118 (7831)	2846.89	74.2% (61.47;83.24)
Northern America	7 (8829)	2599.64	26 (8663)	2469.98	74.4% (39.49;90.63)
Southern Africa	8 (2422)	1230.69	32 (2430)	1225.26	75.1% (44.85;90.09)

Figure S13. Solicited Local (A) and Systemic (B) Adverse Events Reported after Vaccination (Safety Set)

No grade 4 local adverse events were reported; 1 grade 4 systemic adverse event of myalgia was reported in the Ad26.COV2.S group.

Pain was categorized as grade 1 (mild; does not interfere with activity), grade 2 (moderate; requires modification of activity; discomfort with movement), grade 3 (severe; inability to perform usual activities), or grade 4 (potentially life-threatening; hospitalization or inability to perform basic self-care). Erythema and swelling were categorized as grade 1 (mild; 25 to 50 mm), grade 2 (moderate; 51 to 100 mm), grade 3 (severe; more than 100 mm), or grade 4 (potentially life-threatening; necrosis or requiring hospitalization). Systemic events were categorized as grade 1 (mild; minimal symptoms), grade 2 (moderate; notable symptoms not resulting in loss of work or school), grade 3 (severe; incapacitating symptoms resulting in loss of work or school), or grade 4 (life-threatening; hospitalization or inability to perform basic self-care). Fever was defined as grade 1 (mild; ≥38.0°C to 38.4°C), grade 2 (moderate; ≥38.5°C to 38.9°C), grade 3 (severe; ≥39.0°C to 40.0°C), or grade 4 (potentially life-threatening; >40°C).

A

B

Grade 1
Grade 2
Grade 3
100
90
80
70
60
50
40
30
20
10
0
2.3%
0.8%
1.1%
0.3%
0.9%
0.3%
1.1%
0.3%
0.3%
0.3%
0.4%
0%
Ad26.COV2.S
Placebo
Ad26.COV2.S
Placebo
Ad26.COV2.S
Placebo
Ad26.COV2.S
Placebo
Ad26.COV2.S
Placebo
Ad26.COV2.S
Placebo
Any Systemic Event
Fatigue
Headache
Myalgia
Nausea
Fever

SUPPLEMENTARY TABLES

Table S1. Objectives and Endpoints of the Trial

Objectives	Endpoints
Co-Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed*, moderate to severe–critical Covid-19†, as compared to placebo, in SARS-CoV-2 seronegative adults	• First occurrence of molecularly confirmed*, moderate to severe–critical Covid-19†, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed*, moderate to severe–critical Covid-19†, with onset at least 28 days post-vaccination (Day 29)
Secondary‖	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed*, severe–critical Covid-19†, as compared to placebo	• First occurrence of molecularly confirmed*, severe–critical Covid-19†, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed*, severe–critical Covid-19†, with onset at least 28 days post-vaccination (Day 29)
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed*, moderate to severe–critical Covid-19†, as compared to placebo, in adults regardless of their serostatus	• First occurrence of molecularly confirmed*, moderate to severe–critical Covid-19†, with onset 1 day post-vaccination • First occurrence of molecularly confirmed*, moderate to severe–critical Covid-19†, with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed*, moderate to severe–critical Covid-19†, with onset at least 28 days post-vaccination (Day 29)
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed* moderate to severe–critical Covid-19† as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed*, moderate to severe–critical Covid-19† with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on Covid-19 requiring medical intervention (based on objective criteria) compared to placebo	• First occurrence of Covid-19 requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit [ICU] admission, mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomographic [CT] findings) and linked to any molecularly confirmed*, Covid-19†,‡ at least 14 days post-vaccination (Day 15)

	• First occurrence of Covid-19 requiring medical intervention and linked to any molecularly confirmed*, Covid-19†,‡ at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe–critical Covid-19†	Assessment of the SARS-CoV-2 viral load by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR), in participants with molecularly confirmed*, moderate to severe–critical Covid-19† by serial viral load measurements during the course of a Covid-19 episode
To assess the effect of Ad26.COV2.S on molecularly confirmed* mild Covid-19[c]	• First occurrence of molecularly confirmed*, mild Covid-19†, at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed*, mild Covid-19†, at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on Covid-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition §	• First occurrence of molecularly confirmed* Covid-19† at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed* Covid-19† at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on all molecularly confirmed* symptomatic Covid-19†,‡ as compared to placebo	• Burden of disease (BOD) endpoint** derived from the first occurrence of molecularly confirmed* symptomatic Covid-19†,‡ (meeting the mild, moderate or severe–critical Covid-19 case definition) with onset at least 14 days post-vaccination (Day 15). • BOD endpoint** derived from the first occurrence of molecularly confirmed* symptomatic Covid-19†,‡ (meeting the mild, moderate or severe–critical Covid-19 case definition) with onset at least 28 days post-vaccination (Day 29).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein.
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed*), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed*) with onset at least 28 days after vaccination (Day 29)

Safety	
To evaluate safety in terms of serious adverse events (SAEs and AESIs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post- vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs and AESIs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination, and in terms of unsolicited AEs during 28 days post- vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days following vaccination and of unsolicited AEs during 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA
Exploratory (selected)	
To explore the effect of Ad26.COV2.S on other potential complications of Covid-19 (linked to any respiratory disease and linked to any molecularly-confirmed Covid-19) not previously described, as compared to placebo	• First occurrence of potential complications of Covid-19 linked to any respiratory disease and linked to any molecularly confirms Covid-19, with onset at least 14 days after double-blind vaccination (Day 15) • First occurrence of potential complications of Covid-19 linked to any respiratory disease and linked to any molecularly confirms Covid-19, with onset at least 28 days after double-blind vaccination (Day 29)
To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo	• Deaths occurring at least 14 days after double-blind vaccination (Day 15) • Deaths occurring at least 28 days after double-blind vaccination (Day 29)
To evaluate patient-reported outcomes (PROs) in relation to the presence of SARS-CoV-2 infection and the presence, severity and duration of Covid-19 signs and symptoms in participants who received Ad26.COV2.S as compared with placebo	Presence, severity and duration of Covid-19 signs and symptoms Confirmation of SARS-CoV-2 infection by molecular testing
To assess the difference in severity of cases in participants who received Ad25.COV2.S as compared to placebo	Reduction in severity of Covid-19 signs and symptoms

*Molecularly confirmed Covid-19 is defined as a positive SARS-CoV-2 viral RNA result using a RT-PCR assay (Abbott) at the University of Washington.
†Per case definition for moderate to severe–critical Covid-19 (see Section 8.1.3.1 in the protocol).
‡Per case definition for mild Covid-19 (see Section 8.1.3.2 in the protocol).
§Per case definition for Covid-19 according to the US FDA harmonized case definition (see Section 8.1.3.3 in the protocol).

‖All secondary endpoint analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated.
**For more information and the definition of the BOD endpoint, refer to Section 9.5.2 Secondary Endpoints in the protocol.

Table S2. Total Number of Cases of First Occurrence of Molecularly Confirmed Moderate to Severe–Critical Covid-19 with Onset at Least 28 days After Vaccination by SARS-CoV-2 Lineage and by Country (Per-Protocol Set).

	Argentina	Brazil	Chile	Colombia	Mexico	Peru	South Africa	United States
Reference strain	6	2	0	12	1	2	1	75
Lineages other than reference strain	76	183	3	149	2	92	96	51
B.1.1.7 (Alpha)	7	5	0	2	0	1	3	20
B.1.351 (Beta)	0	0	0	0	0	0	69	0
B.1.617.2/AY.1/AY.2 (Delta)	0	0	0	0	0	0	21	0
B.1.427/429 (Epsilon)	0	0	1	1	0	0	0	17
P.1 (Gamma)	43	87	1	28	0	26	0	1
B.1.526 (Iota)	0	0	0	0	0	0	0	4
C.37 (Lambda)	22	0	0	2	0	64	1	0
P.2 (Zeta)	3	86	1	0	0	1	0	1
B.1.621 (Mu)	0	0	0	95	0	0	0	0
R.1	0	0	0	0	0	0	0	1
B.1.1.519	0	0	0	0	2	0	0	4
Other+E484K	1	5	0	21	0	0	2	3
Other	43	26	7	65	1	23	2	112

Table S3. Characteristics of the Trial Participants at Baseline (Full Analysis Set*)

Characteristic	Ad26.COV2.S (N=21,898)	Placebo (N=21,890)	All (N=43,788)
Age − median (range), yr	52.0 (18-100)	52.0 (18-94)	52.0 (18-100)
Age – no. (%)			
18-59 yr	14,564 (66.5)	14,553 (66.5)	29,117 (66.5)
≥60 yr	7334 (33.5)	7337 (33.5)	14,671 (33.5)
Sex – no. (%)			
Female	9828 (44.9)	9907 (45.3)	19,735 (45.1)
Male	12,067 (55.1)	11,979 (54.7)	24,046 (54.9)
Undifferentiated	2 (<0.1)	4 (<0.1)	6 (<0.1)
Unknown	1 (<0.1)	0	1 (<0.1)
Race† – no. (%)			
American Indian or Alaskan Native	2083 (9.5)	2060 (9.4)	4143 (9.5)
Asian	743 (3.4)	686 (3.1)	1429 (3.3)
Black or African American	4253 (19.4)	4262 (19.5)	8515 (19.4)
Native Hawaiian or other Pacific Islander	56 (0.3)	47 (0.2)	103 (0.2)
White	12,858 (58.7)	12,843 (58.7)	25,701 (58.7)
Multiracial	1207 (5.5)	1248 (5.7)	2455 (5.6)
Not reported, unknown or missing	698 (3.2)	744 (3.4)	1442 (3.3)
Ethnicity† − no. (%)			
Hispanic or Latino	9875 (45.1)	9964 (45.5)	19,839 (45.3)
Not Hispanic or Latino	11,476 (52.4)	11,367 (51.9)	22,843 (52.2)
Not reported, unknown or missing	547 (2.5)	559 (2.6)	1106 (2.5)
Country/region – no. (%)			
Latin America	8954 (40.9)	8952 (40.9)	17,906 (40.9)
Argentina	1498 (6.8)	1498 (6.8)	2996 (6.8)
Brazil	3644 (16.6)	3635 (16.6)	7279 (16.6)
Chile	563 (2.6)	570 (2.6)	1133 (2.6)
Colombia	2125 (9.7)	2123 (9.7)	4248 (9.7)
Mexico	238 (1.1)	241 (1.1)	479 (1.1)
Peru	886 (4.0)	885 (4.0)	1771 (4.0)
South Africa	3287 (15.0)	3289 (15.0)	6576 (15.0)
United States	9657 (44.1)	9649 (44.1)	19,306 (44.1)

SARS-CoV-2 serostatus – no. (%)			
Positive	2172 (9.9)	2103 (9.6)	4275 (9.8)
Negative	19,503 (89.1)	19,587 (89.5)	39,090 (89.3)
Missing	223 (1.0)	200 (0.9)	423 (1.0)
Body-mass index‡			
Median	27.0	27.0	27.0
≥30 – no. (%)	6264 (28.6)	6227 (28.5)	12,491 (28.5)
One or more comorbidity at baseline – no. (%)	9194 (42.0)	9203 (42.0)	18,397 (42.0)

*The full analysis set included all those participants who were randomized and received a documented dose of Ad26.COV2.S vaccine or placebo, regardless of serostatus at enrollment.
†Race and ethnicity were self-reported by participants.
‡Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. A BMI equal to or greater than 30 indicates obesity.
SARS-CoV-2, severe acute respiratory coronavirus 2.

Table S4. Representativeness of Study Participants

Category		Characteristic	Unites States population, reported cases (%)	United States demographics of recruited study population in COV3001 (%)	Overall demographics of recruited study population in COV3001 (%)*
Disease, problem, or condition	Covid-19				
Special considerations					
Sex	Male sex is a factor associated with ICU admission and in-hospital mortality resulting from Covid-19 infection.†	**Sex‡**			
		Male	47.6	55.7	54.9
		Female	52.3	44.3	45.1
Age	Age ≥65 years has been shown to be the strongest independent risk factor for Covid-19-related ICU admission and mortality.†	**Age‡**			
		18-64 years	71.7	75.8	80.4
		≥65 years	12.4	24.2	19.5
Race	Covid-19 has disproportionately affected people of color.§ However, among those hospitalized, race was not reported to be associated with risk of poorer outcomes related to Covid-19.†	**Race‡**			
		American Indian or Alaskan Native	1.1	1.0	9.5
		Asian	3.2	6.5	3.3
		Black or African American	11.8	13.0	19.4
		Native Hawaiian/Pacific Islander	0.3	0.4	0.2
		White	55.6	73.6	58.7
		Multiracial	3.8	1.9	5.6
Ethnicity	Covid-19 has impacted a disproportionate number of Hispanic/Latino individuals.§	**Ethnicity‡**			
		Hispanic or Latino	24.3	14.7	45.3
Geography	Covid-19 is a global pandemic.	**Region**	COV3001 enrolled participants in Latin America (40.9%), South Africa (15.0%), and the United States (44.1%)		

Category		Characteristic	Unites States population, reported cases (%)	United States demographics of recruited study population in COV3001 (%)	Overall demographics of recruited study population in COV3001 (%)*
Other considerations	A higher number of underlying comorbidities increases risk of ICU admission and mortality in the United States.† Diabetes, obesity, and immunosuppression are associated with ICU admission. Diabetes, chronic lung disease, cardiovascular disease, neurologic disease, renal disease and immunosuppression are associated with in-hospital death.†	Obesity†	49.7	32.0	28.7
		Diabetes†	32.9	8.1	7.8
		Renal disease/chronic kidney disease†	15.5	0.8	0.5
		Neurologic disease/conditions†	22.1	0.9	0.6
		Hypertension‖	50.4	12.5	10.9
		Chronic obstructive pulmonary disease†	10.7	1.4	1.0
		Asthma†	12.6	2.1	1.4
Overall representativeness of this trial		The COV3001 trial enrolled a slightly higher proportion of male participants versus female in both the United States and globally. Based on data from the CDC, more cases in the United States have occurred in female versus male individuals.‡ A study on risk factors in the United States has shown that men are at higher risk for ICU admission and mortality from Covid-19.† Persons aged greater than 65 years were represented at a greater proportion in our trial relative to the total United States population at risk of Covid-19 infection.‡ Our trial enrolled participants in 8 countries to ensure risk factors of race and ethnicity were adequately addressed. Overall, the proportion of participants (both globally and in the United States) in this trial with underlying comorbidities was lower than what is reported in a United States population evaluated for hospitalization/mortality risk factors.† Our enrollment strategy utilized the CDC guidelines for comorbidities that might be associated with increased risk of progression to Covid-19.‖			

*Some characteristics of the study population were by design, as the trial was enriched for high at-risk participation (e.g., targeting 30% >60 years of age and recruitment across geographical distributions).

†Derived for the United States population from Kim L, Garg S, O'Halloran A, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis*. 2021;72(9):e206-e214. doi:10.1093/cid/ciaa1012

‡https://covid.cdc.gov/covid-data-tracker/#demographics.

§https://covidtracking.com/race.

‖Hypertension in hospitalized patients with Covid-19 representative of the overall United States population was obtained from Kompaniyets L, et al. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020-March 2021. Prev Chronic Dis. 2021 Jul 1;18:E66. doi: 10.5888/pcd18.210123. PMID: 34197283; PMCID: PMC8269743.
‖https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.
CDC, Centers for Disease Control and Prevention; ICU, intensive care unit; N/A, not applicable.

Table S5. Vaccine Efficacy Against Covid-19 by Serostatus at Baseline (Post Hoc Analysis; Per-Protocol, Risk Set*)

Serostatus at Baseline	At Least 14 Days after Vaccination					At Least 28 Days after Vaccination				
Seropositive (Ad26.COV2.S) vs. Seropositive (Placebo)†	**Ad26.COV2.S Seropositive (N=2137)**		**Placebo Seropositive (N=2069)**		**Vaccine Efficacy (95% CI)**	**Ad26.COV2.S Seropositive (N=2131)**		**Placebo Seropositive (N=2054)**		**Vaccine Efficacy (95% CI)**
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	*%*	*no. of cases*	*person-yr*	*no. of cases*	*person-yr*	*%*
Moderate to severe–critical	3	956.4	12	908.8	76.2 (12.0-95.7)	3	955.6	12	907.0	76.3 (12.1-95.7)
Moderate	3	956.4	12	908.8	76.2 (12.0-95.7)	3	955.6	12	907.0	76.3 (12.1-95.7)
Severe–critical	0	957.3	0	912.1	N/E	0	956.4	0	910.2	N/E
Seropositive (Placebo) vs. Seronegative (Placebo)‡	**Placebo Seropositive (N=2069)**		**Placebo Seronegative (N=19398)**		**Vaccine Efficacy (95% CI)**	**Placebo Seropositive (N=2054)**		**Placebo Seronegative (N=18924)**		**Vaccine Efficacy (95% CI)**
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	*%*	*no. of cases*	*person-yr*	*no. of cases*	*person-yr*	*%*
Moderate to severe–critical	12	908.8	1067	6440.2	92.0 (83.9-95.9)	12	907.0	883	6400.4	90.4 (83.2-95.1)
Seropositive (Ad26.COV.S) vs. Seronegative (Placebo)‡	**Ad26.COV2.S Seropositive (N=2137)**		**Placebo Seronegative (N=19398)**		**Vaccine Efficacy (95% CI)**	**Ad26.COV2.S Seropositive (N=2131)**		**Placebo Seronegative (N=18924)**		**Vaccine Efficacy (95% CI)§**
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	*%*	*no. of cases*	*person-yr*	*no. of cases*	*person-yr*	*%*
Moderate to severe–critical	3	956.4	1067	6440.2	98.1 (94.5-99.6)	3	955.6	883	6400.4	97.7 (93.3-99.5)

*The risk set excluded participants who had a Covid-19 case with an onset before day 15 (for vaccine efficacy evaluation at least 14 days after vaccination) or before day 29 (for vaccine efficacy evaluation at least 28 days after vaccination).

†Descriptive 95% CI.

‡Prespecified in the Statistical Analysis Plan, but not included in the scheme for family-wise type I error control, summarized with descriptive 95% CIs.

§Post hoc analysis.

CI, Confidence Interval; N/E, Not Evaluable.

Table S6. Vaccine Efficacy Against Moderate to Severe–Critical Covid-19 with Onset 28 Days After Vaccination in Hispanic and Asian Populations, by SARS-CoV-2 Lineage and Country (Post Hoc Analysis)

Cases in Hispanic Participants, n	**Ad26.COV2.S** Participants, N=8632	**Placebo** Participants, N=8658	**Vaccine Efficacy (95% CI)**
Reference strain	13	23	45.0 (-13.2-74.4)
By SARS-CoV-2 lineage			
Alpha	5	14	65.3 (-2.0-90.2)
Beta	0	1	
Delta	1	0	
Epsilon	3	5	41.7 (-199.9-90.9)
Gamma	67	108	39.7 (17.4-56.2)
Lambda	43	44	5.0 (-48.1-39.1)
Zeta	24	63	63.0 (39.9-77.9)
Mu	38	57	35.2 (0.6-58.2)
R.1	1	0	
B.1.1.519	0	2	
Other+E48K	8	20	61.1 (7.8-85.2)
Other	45	125	65.0 (50.4-75.7)
By country/region			
US	13	38	66.2 (35.2-83.5)
Latin America	302	536	45.3 (36.9-52.7)
South Africa	1	1	
Cases in Asian Participants, n	**Ad26.COV2.S** Participants, N=669	**Placebo** Participants, N=607	**Vaccine Efficacy (95% CI)**
Reference strain	0	2	
By SARS-CoV-2 lineage			
Beta	1	0	
Epsilon	1	4	
Gamma	4	1	
By country/region			
US	3	11	76.6% (11.4-95.8)
Latin America	5	1	-423.3% (-24652.7- 41.4)
South Africa	2	0	

Sequences categorized as "Other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. CI, confidence interval.

Table S7. Unsolicited Adverse Events of Grade ≥3 Severity (Safety Set)

	Ad26.COV2.S N=3356	Placebo N=3380
AEs, n (%)		
Participants with ≥1 unsolicited AE	27 (0.8)	23 (0.7)
Nervous system disorders	6 (0.2)	5 (0.1)
Headache	3 (0.1)	1 (<0.1)
Cerebral hemorrhage	1 (<0.1)	0
Epilepsy	1 (<0.1)	0
Generalized tonic-clonic seizure	1 (<0.1)	0
Metabolic encephalopathy	1 (<0.1)	0
Transverse sinus thrombosis	1 (<0.1)	0
Anosmia	0	1 (<0.1)
Dizziness	0	2 (0.1)
Motor dysfunction	0	1 (<0.1)
Syncope	0	1 (<0.1)
Tension headache	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	4 (0.1)	4 (0.1)
Allergic cough	1 (<0.1)	0
Asthma	1 (<0.1)	0
Cough	1 (<0.1)	0
Dyspnea	1 (<0.1)	0
Nasal congestion	1 (<0.1)	2 (0.1)
Sneezing	1 (<0.1)	2 (0.1)
Oropharyngeal pain	0	2 (0.1)
Sinus congestion	0	1 (<0.1)
Wheezing	0	1 (<0.1)
General disorders and administration site conditions	3 (0.1)	3 (0.1)
Chest pain	1 (<0.1)	0
Fatigue	1 (<0.1)	2 (0.1)
Pain	1 (<0.1)	0
Malaise	0	2 (0.1)
Gastrointestinal disorders	2 (0.1)	1 (<0.1)
Diarrhea	2 (0.1)	0
Ulcerative colitis	0	1 (<0.1)
Infections and infestations	2 (0.1)	7 (0.2)
Diverticulitis	1 (<0.1)	0
Tonsillitis	1 (<0.1)	0
Covid-19	0	4 (0.1)
Covid-19 pneumonia	0	1 (<0.1)

Lower respiratory tract infection	0	1 (<0.1)
Mastitis	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	2 (0.1)	5 (0.1)
Arthralgia	1 (<0.1)	2 (0.1)
Back pain	1 (<0.1)	0
Pain in extremity	1 (<0.1)	0
Muscle tightness	0	1 (<0.1)
Myalgia	0	2 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.1)	0
Pancreatic neoplasm	1 (<0.1)	0
Prostate cancer	1 (<0.1)	0
Renal and urinary disorders	2 (0.1)	1 (<0.1)
Nephrolithiasis	2 (0.1)	0
Ureterolithiasis	0	1 (<0.1)
Blood and lymphatic system disorders	1 (<0.1)	0
Thrombocytopenia	1 (<0.1)	0
Cardiac disorders	1 (<0.1)	0
Myocardial infarction	1 (<0.1)	0
Hepatobiliary disorders	1 (<0.1)	0
Cholelithiasis	1 (<0.1)	0
Metabolism and nutrition disorders	1 (<0.1)	0
Gout	1 (<0.1)	0
Pregnancy, puerperium and perinatal conditions	1 (<0.1)	0
Abortion spontaneous	1 (<0.1)	0
Skin and subcutaneous tissue disorders	1 (<0.1)	0
Guttate psoriasis	1 (<0.1)	0
Eye disorders	0	1 (<0.1)
Eye pain	0	1 (<0.1)
Psychiatric disorders	0	2 (0.1)
Substance dependence	0	1 (<0.1)
Suicidal ideation	0	1 (<0.1)
Reproductive system and breast disorders	0	1 (<0.1)
Heavy menstrual bleeding	0	1 (<0.1)
Vascular disorders	0	2 (0.1)
Hypertension	0	2 (0.1)

The safety subset comprised approximately 6,000 participants who recorded solicited local and systemic adverse events in an electronic diary for 7 days post-vaccination and unsolicited AEs for 28 days post-vaccination. Participants were counted only once within the period for any given event, regardless of the number of times they experienced the event within the period. Adverse events were coded using MedDRA Version 24.0.
AEs, adverse events.

Table S8. Unsolicited Adverse Events of Grade ≥3 Severity Considered Related to Ad26.COV2.S or Placebo (Full Analysis and Safety Sets)

	Number (%) Participants	
	Ad26.COV2.S	**Placebo**
Full Analysis Set	**N=21,898**	**N=21,890**
Participants with ≥1 AE, n (%)	20 (0.1)	11 (0.1)
Nervous system disorders	9 (<0.1)	3 (<0.1)
Headache	6 (<0.1)	2 (<0.1)
Complex regional pain syndrome	1 (<0.1)	0
Guillain-Barré Syndrome	1 (<0.1)	0
Syncope	1 (<0.1)	0
Dizziness	0	1 (<0.1%)
General disorders and administration site conditions	5 (<0.1)	3 (<0.1)
Fatigue	3 (<0.1)	3 (<0.1)
Chest pain	1 (<0.1)	0
Feeling abnormal	1 (<0.1)	0
Pyrexia	1 (<0.1)	0
Asthenia	0	1 (<0.1)
Malaise	0	1 (<0.1)
Gastrointestinal disorders	3 (<0.1)	2 (<0.1)
Diarrhea	1 (<0.1)	1 (<0.1)
Dyspepsia	1 (<0.1)	0
Nausea	1 (<0.1)	0
Abdominal pain	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	2 (<0.1)	1 (<0.1)
Dyspnea	1 (<0.1)	0
Nasal congestion	1 (<0.1)	1 (<0.1)
Sneezing	0	1 (<0.1)
Wheezing	0	1 (<0.1)
Cardiac disorders	1 (<0.1)	2 (<0.1)
Pericarditis	1 (<0.1)	0
Atrial fibrillation	0	1 (<0.1)
Atrial flutter	0	1 (<0.1)
Immune system disorders	1 (<0.1)	0
Hypersensitivity	1 (<0.1)	0
Injury, poisoning and procedural complications	1 (<0.1)	0
Post-vaccination syndrome	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	1 (<0.1)	3 (<0.1)
Myalgia	1 (<0.1)	1 (<0.1)
Arthralgia	0	1 (<0.1)
Back pain	0	1 (<0.1)
Ear and labyrinth disorders	0	1 (<0.1)
Vertigo	0	1 (<0.1)
Infections and infestations	0	1 (<0.1)
Epstein-Barr virus	0	1 (<0.1)
Vascular disorders	1 (<0.1)	0
Deep vein thrombosis	1 (<0.1)	0

	Number (%) Participants	
	Ad26.COV2.S	**Placebo**
Skin and subcutaneous tissue disorders	0	1 (<0.1)
Dermatitis	0	1 (<0.1)
Safety set	**N=3356**	**N=3380**
Participants with ≥1 AE, n (%)	5 (0.1)	2 (0.1)
Nervous system disorders	3 (0.1)	1 (<0.1)
Headache	3 (0.1)	0
Dizziness	0	1 (<0.1)
Gastrointestinal disorders	1 (<0.1)	0
Diarrhea	1 (<0.1)	0
General disorders and administration site conditions	1 (<0.1)	1 (<0.1)
Fatigue	1 (<0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	1 (<0.1)
Arthralgia	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1)
Nasal congestion	0	1 (<0.1)
Sneezing	0	1 (<0.1)
Wheezing	0	1 (<0.1)

The safety subset comprised approximately 6,000 participants who recorded solicited local and systemic adverse events in an electronic diary for 7 days post-vaccination and unsolicited AEs for 28 days post-vaccination.
AE, adverse event.

Table S9. Summary of SAEs and Deaths (Full Analysis Set)

	Ad26.COV2.S	Placebo
SAEs, n (%)	N=21,898	N=21,890
Participants with ≥1 SAE not related to Covid-19	223 (1.0)	265 (1.2)
Participants with SAE considered by the investigator to be related to vaccination	19	2
Ischemic stroke*	3	0
Bell's palsy*	2	0
Deep vein thrombosis*	2	0
Pulmonary embolism*	2†	0
Asthma	1	0
Atrial fibrillation*	1	0
Complex regional pain syndrome	1	0
Guillain-Barré syndrome	1	0
Headache*	1	0
Hypersensitivity	1	0
Pericarditis	1	0
Post-vaccination syndrome	1	0
Retinal vein thrombosis*	1	0
Venous thrombosis*	1†	0
Epstein-Barr virus infection*	0	1‡
Atrial flutter*	0	1‡
Deaths		
Deaths§	28	55
Covid-19 related deaths‖	5	22

*Considered "not related" to vaccination by the sponsor.
†One SAE of pulmonary embolism and venous thrombosis occurred in the same participant.
‡ Epstein-Barr virus infection and atrial flutter occurred in the same participant.
§ Deaths reported in the double-blind phase.
‖COVID-19 related deaths reported in the full analysis set; in the per-protocol set, there were 3 COVID-19 related deaths in the vaccine group and 17 deaths in the placebo group 28 days after vaccination.
SAEs, serious adverse events.

Table S10. Adverse Events of Clinical Interest and of Special Interest

	28-Day Period after Vaccination		Entire Double-blind Phase	
	Ad26.COV2.S N=21,894	**Placebo** N=21,882	**Ad26.COV2.S** N=21,894	**Placebo** N=21,882
AEs of clinical interest, n (%)				
Thrombotic and Thromboembolic Events	14 (0.1)	10 (<0.1)	40 (0.2)	36 (0.2)
Embolic and thrombotic events, arterial				
Acute myocardial infarction	0	2 (<0.1)	2 (<0.1)	7 (<0.1)
Myocardial infarction	1 (<0.1)	0	2 (<0.1)	3 (<0.1)
Transient ischemic attack	0	0	2 (<0.1)	3 (<0.1)
Carotid artery occlusion	0	1 (<0.1)	0	1 (<0.1)
Peripheral artery occlusion	0	0	0	1 (<0.1)
Blindness transient	1 (<0.1)	0	1 (<0.1)	0
Ischemic stroke	1 (<0.1)	0	3 (<0.1)	0
Embolic and thrombotic events, venous				
Pulmonary embolism	2 (<0.1)	2 (<0.1)	10 (<0.1)	5 (<0.1)
Deep vein thrombosis	4 (<0.1)	2 (<0.1)	11 (0.1)	3 (<0.1)
Cerebral venous sinus thrombosis	0	0	0	1 (<0.1)
Thrombophlebitis	0	0	0	1 (<0.1)
Embolism venous	0	0	1 (<0.1)	0
Retinal vein thrombosis	0	0	1 (<0.1)	0
Thrombophlebitis superficial	0	0	1 (<0.1)	0
Transverse sinus thrombosis	1 (<0.1)	0	1 (<0.1)	0
Venous thrombosis limb	1 (<0.1)	0	1 (<0.1)	0
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous				
Cerebrovascular accident	0	0	4 (<0.1)	6 (<0.1)
Cerebral infarction	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Hemiparesis	2 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)

Embolism	0	0	0	1 (<0.1)
Hemiplegia	0	0	1 (<0.1)	1 (<0.1)
Paraparesis	0	0	0	1 (<0.1)
Vascular stent occlusion	0	0	0	1 (<0.1)
Brain stem stroke	1 (<0.1)	0	1 (<0.1)	0
Thrombocytopenia	1 (<0.1)	1 (<0.1)	1 (<0.1)	8 (<0.1)
Immune thrombocytopenia	0	0	0	1 (<0.1)
Tinnitus	9 (<0.1)	0	15 (0.1)	4 (<0.1)
Urticaria	8 (<0.1)	3 (<0.1)	13 (<0.1)	6 (<0.1)
Convulsions/Seizures	4 (<0.1)	0	9 (<0.1)	4 (<0.1)
Guillain-Barré syndrome	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Bell's Palsy	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Pericarditis	1 (<0.1)	0	1 (<0.1)	0
Adverse event of special interest*				
Thrombosis with thrombocytopenia	1 (<0.1)	0	1 (<0.1)	0

*One event had a positive anti PF4 antibody and met the CDC Tier 1 and Brighton Collaboration Level 1 criteria for thrombosis with thrombocytopenia, as confirmed by an adjudication committee.
AE, adverse event; SAE, serious adverse event.

SUPPLEMENTARY REFERENCES

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