Janssen Vaccines & Prevention B.V.*

Clinical Protocol

Protocol Title

A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older

ENSEMBLE 2

Protocol VAC31518COV3009; Phase 3
AMENDMENT 3

VAC31518 (JNJ-78436735)

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study. The sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number:

IND: 22657

EudraCT: 2020-003643-29

Status: Approved
Date: 18 December 2020
EDMS number: EDMS-RIM-96655, 4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	This document
Amendment 2	27 November 2020
Amendment 1	25 September 2020
Original Protocol	22 August 2020

Amendment 3 (This document)

Overall Rationale for the Amendment: The main purpose of this amendment is to outline the procedures to be followed in the event that an investigator receives a request to unblind study participants who may become eligible to receive an authorized/licensed COVID-19 vaccine if/when these become available. The purpose is to ensure (1) that the participants are informed that there is no data on the safety of receiving two different COVID-19 vaccines, (2) that in the event the participant is unblinded, no further study vaccination will be permitted, (3) that unblinded participants will continue to be followed in this study in line with the Schedules of Activities, and that safety, efficacy, and immunogenicity evaluations will continue to be performed, although the data will be analyzed separately from the point of unblinding.

The changes made to the clinical protocol of study VAC31518COV3009 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine After the End of the Study 7.1 Discontinuation of Study vaccination 9.9 Analyses for cohort unblinded due to administration of an authorized/licensed COVID-19 vaccine.	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.	To ensure that if participants become eligible to receive an authorized/licensed COVID-19 vaccine, they are aware of the potential options and ramifications, including the lack of safety data of the authorized/licensed vaccine in participants that have received a 1-dose or 2-dose Ad26.COV2.S vaccine, and that no further study vaccination will be permitted; that unblinded participants will continue to be followed throughout the study for safety, efficacy and immunogenicity assessments, although the data will be analyzed separately from the point of unblinding.
7.1 Discontinuation of Study vaccination	Clarification that study vaccination will be discontinued in participants with molecularly confirmed SARS-CoV-2 infection, regardless of symptomatic or asymptomatic.	Clarification

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.1.4 Immunogenicity Assessments	psVNA was removed from the protocol. wtVNA will be used to support the exploratory immunogenicity endpoint.	Due to lack of sensitivity of the evaluated psVNA, the assay has been removed from the protocol wtVNA is currently only qualified and not validated and can therefore not be used to support a secondary immunogenicity endpoint unless validated.
5.1 Inclusion Criteria	Inclusion criterion 4 was updated to include a timeframe for criteria a and b for stable/well-controlled HIV infection. In addition, it was clarified that participants with stable/well-controlled HIV infection that are on stable ART are included if nationwide guidelines require transition from one ART regimen to another, within a period of less than 6 months	Clarification
5.2 Exclusion Criteria	Exclusion criterion 4 updated for clarification.	Clarification
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Minor clarifications are made.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older

Ad26.COV2.S (previously known as Ad26COVS1) is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein.

Information about the disease, correlates of immunity, and safety issues concerning this new pandemic-causing virus are rapidly evolving. Therefore, it is critical to recognize that the approach outlined in this document might or will change as insights and discussions evolve.

OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and endpoints are:

Objectives	Endpoints
Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical coronavirus disease-2019 (COVID-19)[b], as compared to placebo, in SARS-CoV-2 seronegative adults	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days after the 2nd vaccination (Day 71)
Secondary[c] *(The method used to perform hypothesis testing preserving the family-wise error rate [FWER] will be specified in the Statistical Analysis Plan [SAP])*	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b], as compared to placebo, in adults regardless of their serostatus	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 1 day after the 1st vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days after the 2nd vaccination (Day 71)
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b] as compared to placebo	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after the 1st vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 14 days after the 1st vaccination (Day 15)
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[a], COVID-19[b,c] at least 14 days after the 2nd vaccination (Day 71)

Objectives	Endpoints
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[b]	Assessment of the SARS-CoV-2 viral load by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR), in participants with molecularly confirmed[a], moderate to severe/critical COVID-19[b] by serial viral load measurements during the course of a COVID-19 episode, at least 14 days after the 2nd vaccination (Day 71)
To assess the effect of Ad26.COV2.S on molecularly confirmed[a] mild COVID-19[c]	First occurrence of molecularly confirmed[a], mild COVID-19[c], at least 14 days after the 2nd vaccination (Day 71)
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[d]	First occurrence of molecularly confirmed[a] COVID-19[d] at least 14 days after the 2nd vaccination (Day 71)
To assess the effect of Ad26.COV2.S on all molecularly confirmed symptomatic COVID-19[b,c], as compared to placebo	Burden of disease (BOD) endpoint[f] derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 14 days after the 2nd vaccination (Day 71)
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; before 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd 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[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 14 days after the 2nd vaccination (Day 71)
Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months after the last vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months after the last vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants
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 each vaccination, and in terms of unsolicited AEs during 28 days after each vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days following each vaccination and of unsolicited AEs during 28 days following each vaccination

Objectives	Endpoints
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

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result by a central laboratory using a PCR-based or other molecular diagnostic test.
[b] Per case definition for moderate to severe/critical COVID-19 (see below).
[c] Per case definition for mild COVID-19 (see below).
[d] Per US FDA harmonized case definition for COVID-19 (see below).
[e] All secondary efficacy endpoint analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated in the statistical analysis plan (SAP).
[f] For more information and the definition of the BOD endpoint, refer to the body of the protocol.

Exploratory objectives and endpoints, including correlates of protection, evaluation of efficacy in seropositive participants and/or participants with a SARS-CoV-2 positive RT-PCR or molecular test result, are included in the body of this protocol.

Hypotheses

The study is designed to test the primary hypothesis of vaccine efficacy (VE) in the PP population: H0: VE ≤30% versus H1: VE >30% and will be evaluated at a 2.5% one-sided significance level.

The primary endpoint will evaluate the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition, with onset at least 14 days after the 2nd vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events with and without comorbidities.

If the primary endpoint hypothesis testing is successful, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%. The method to perform hypothesis testing of primary and secondary objectives preserving the family-wise error rate (FWER) will be specified in the SAP. The FWER will be controlled at 2.5% one-sided significance level.

Case Definitions

The severity of all COVID-19 cases will be assessed independently by a clinical evaluation committee (CEC). This committee is not an endpoint adjudication committee but will independently evaluate the severity of the COVID-19 cases. Classification of the severity will be based on the highest degree of severity during the observation period. The criteria for suspected COVID-19 are described in the body of the protocol. As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19.

Case Definition for Moderate to Severe/Critical COVID-19

For the primary endpoint (see above), all moderate and severe/critical COVID-19 cases will be considered.

Case Definition for Moderate COVID-19

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

AND at any time during the course of observation[a]:

Any 1 of the following new or worsening signs or symptoms:		**Any 2 of the following new or worsening signs or symptoms:**
• Respiratory rate ≥20 breaths/minute • Abnormal saturation of oxygen (SpO_2) but still >93% on room air at sea level* • Clinical or radiologic evidence of pneumonia • Radiologic evidence of deep vein thrombosis (DVT) • Shortness of breath or difficulty breathing	**OR**	• Fever (≥38.0°C or ≥100.4°F) • Heart rate ≥90 beats/minute • Shaking chills or rigors • Sore throat • Cough • Malaise as evidenced by 1 or more of the following**: - Loss of appetite - Generally unwell - Fatigue - Physical weakness • Headache • Muscle pain (myalgia) • Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)** • New or changing olfactory or taste disorders • Red or bruised looking feet or toes

* SpO_2 criteria will be adjusted according to altitude per the investigator judgement.
** Having 2 or more elements of a symptom (eg, vomiting and diarrhea or fatigue and loss of appetite) is counted only as 1 symptom for the case definition. To meet the case definition, a participant would need to have at least 2 different symptoms.

Case Definition for Severe/Critical COVID-19

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

AND any 1 of the following at any time during the course of observation[a]:

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

  * SpO_2 criteria will be adjusted according to altitude per the investigator judgement.
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to the ICU
- Death

[a] Participants will be asked to undertake the COVID-19 procedures until 14 days after symptom onset (COVID-19 Day 15) or until **resolution of the COVID-19 episode**, whichever comes last (see Section 8.1.2).

Case Definition for Mild COVID-19

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

  AND at any time during the course of observation[a]:

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

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

US FDA Harmonized Case Definition for COVID-19

If a participant presents with symptoms as those listed by the US FDA harmonized case definition (see appendix to the protocol), the investigator (or designated medically trained clinician) should assess if these are suggestive of COVID-19:

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample; **AND**
- COVID-19 symptoms consistent with those defined by the US FDA harmonized case definition at the time of finalization of this protocol: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.

Case Definition for Asymptomatic or Undetected COVID-19

If a participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms

AND

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

OR

- develops a positive serology (non-S protein) test

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

OVERALL DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.CoV2.S will be evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine.

Initial immunogenicity and safety data (28 days post-Dose 1 data from Cohort 1a and available data from Cohort 3) from study VAC31518COV1001 have demonstrated that a single dose of Ad26.COV2.S at 5×10^{10} virus particles (vp) and 1×10^{11} vp induces an immune response that meets prespecified minimum criteria and has an acceptable safety profile. The sponsor has therefore decided to proceed with an

[a] Participants will be asked to undertake the COVID-19 procedures until 14 days after symptom onset (COVID-19 Day 15) or until **resolution of the COVID-19 episode**, whichever comes last (see Section 8.1.2).

Ad26.COV2.S dose level of 5×10^{10} vp in its Phase 3 studies. Even though a single-dose regimen in study VAC31518COV1001 showed good immunogenicity that may already protect against COVID-19, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in an increased and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study. The single dose regimen will be further evaluated in study VAC31518COV3001.

Participants will be randomized in parallel in a 1:1 ratio to receive Ad26.COV2.S or placebo intramuscularly (IM) as shown in the table below. Ad26.COV2.S will be administered at a dose level of 5×10^{10} vp.

Vaccination Schedule VAC31518COV3009

Group	N	Day 1	Day 57
1	15,000	Ad26.COV2.S (5×10^{10} vp)	Ad26.COV2.S (5×10^{10} vp)
2	15,000	Placebo	Placebo

N = number of participants; vp = virus particles.

Note: It is intended that a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be ≥18 to <40 years of age

A staggered enrollment strategy will be used:

- Stage 1: Initially, approximately 1,000 participants without comorbidities that are associated with increased risk of progression to severe COVID-19 (including approximately 500 Ad26.COV2.S recipients and approximately 500 placebo recipients) will be enrolled.
- Stage 2: After a vaccination pause in Stage 1 to allow the Independent Data Monitoring Committee (IDMC) to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing studies), if no safety concerns are identified enrollment will proceed, expanding enrollment to include participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19 in 2 age-dependent subgroups (≥18 years to <60 years of age and ≥60 years of age).

Comorbidities (or risk factors) that are or might be associated with an increased risk of progression to severe COVID-19[a] include: moderate-to-severe asthma; chronic lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension; moderate to severe high blood pressure; obesity (body mass index [BMI] ≥30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; human immunodeficiency virus (HIV) infection and other immunodeficiencies; hepatitis B infection; sleep apnea; and participants who live in nursing homes or long-term care facilities.

The duration of individual participation, including screening, will be maximum 2 years and 3 months. If a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted. The end-of-study is considered as the completion of the last visit for the last participant in the study.

Key efficacy assessments include the surveillance for COVID-19-like signs and symptoms, recording of COVID-19-related hospitalizations and complications, and the laboratory confirmation of SARS-CoV-2

[a]Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19) Groups at Higher Risk for Severe Illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html. (Accessed: 19 July 2020). In this study, former or current smoking/vaping and mild hypertension (according to the Toxicity Grading Scale in the body of this document) will not be considered as a comorbidity. Gestational diabetes was deleted from the list since it is not applicable as pregnant women are not to participate in the study.

infection by a molecular assay (based on RT-PCR) and by anti-SARS-CoV-2 serology. Immunogenicity assessments, and especially assessments of the humoral immune responses with emphasis on neutralizing and binding antibodies will also be performed. Key safety assessments will include the monitoring of solicited and unsolicited AEs (in the Safety Subset only), and the collection of SAEs and MAAEs in all participants. The viral load of SARS-CoV-2 will be assessed in confirmed COVID-19 cases. Medical resource utilization (MRU) following vaccination will be recorded for all participants with molecularly confirmed, symptomatic COVID-19. Additional characteristics related to current work situation, living situation, and community interactions will be collected for risk factor analysis, if allowed per local regulations. For consenting participants in the US, medical data (electronic health records, claims and laboratory data from other care settings) from 5 years prior to study enrollment until 5 years after study completion may be accessed utilizing tokenization and matching procedures (ie, the generation of anonymous identifiers or "tokens" [hashed and encrypted combinations of identifying elements] to allow linking of participant data from different sources without compromising the participant's confidentiality). These data together with data collected as part of the study (as specified in the Schedules of Activities), may be used for exploratory analyses to enhance our understanding of the impact of prior medical history on the response to immunization and the impact of immunization on efficacy and duration of efficacy as well as adverse events that may occur during and after completion of the study.

Until 1 year after the 2nd vaccination, each participant will be asked at least twice a week, through the electronic clinical outcome assessment (eCOA), if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. As of 1 year after the 2nd vaccination, until the end of the 2-year follow-up period, the frequency of this (suspected) COVID-19 surveillance (symptom check) through the eCOA will decrease to once every 2 weeks. All participants will be monitored for safety (including enhanced disease) for 2 years after the last vaccination, ie, until the last study visit. Every effort will be made to document the status of all participants that are lost to follow-up due to not completing the eCOA and for whom hospitalization has not been recorded.

Enrolled participants will be counselled on SARS-CoV-2 infection prevention each time that they have a contact with site staff, in line with local guidelines. At the time of study entry, each participant will need to indicate to the study site, in case they would get infected with SARS-CoV-2, the identity and location of their routine medical care physician and/or facility and the identity and location of where they would obtain emergency care and hospitalization if necessary. If this information is not available, a plan for where such care could be obtained should be developed. If a participant should have COVID-19 and their symptoms deteriorate, they will be instructed to go to the Health Care Professional (HCP) or hospital that has been identified in advance.

All participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19[a] and all participants with at least one positive RT-PCR test for SARS-CoV-2 on COVID-19 Day 1-2 and Day 3-5 visits should undertake the COVID-19 procedures until 14 days after symptom onset (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last. However, participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19[a] should stop the COVID-19 procedures as soon as it is confirmed that both nasal swabs collected on COVID-19 Day 1-2 and Day 3-5 are negative for SARS-CoV-2. Resolution of the COVID-19 episode is defined as having 2 consecutive SARS-CoV-2 negative nasal swabs and 2 consecutive days with no COVID-19-related signs or symptoms. At the time of resolution of the COVID-19 episode, the collected information will be applied against the clinical case definition.

All necessary precautions (as per local regulation) should be taken to protect medical staff and other contacts of participants who are suspected to have COVID-19 until proven negative by molecular

[a] As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19.

techniques or who are positive AND meet the prespecified criteria for suspected COVID-19 on COVID-19 Day 1-2 and Day 3-5 until they are no longer positive. In the event of a confirmed SARS-CoV-2 infection, the participant and participant's medical care provider and/or local health authorities (if required) will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

An IDMC will be commissioned for this study.

NUMBER OF PARTICIPANTS

Overall, a target of 30,000 adult participants (≥18 to <60 years of age and ≥60 years of age, with and without relevant comorbidities) will be randomly assigned in this study, under the assumption that the annualized incidence of moderate to severe/critical COVID-19 (meeting the COVID-19 case definition for the primary endpoint) will be approximately 1% to 4% at the start of the study. Every effort will be made to identify regions of high SARS-CoV-2 activity and populations within these regions with high risk of exposure to the virus will be enrolled. Recruitment for high incidence populations will also take into account age. Per stage, participants will be enrolled in 2 subgroups (≥18 to <60 years of age and ≥60 years of age). Enrollment may be stopped if the primary endpoint is reached.

This sample size takes into consideration the uncertainty of the epidemiological situation in combination with the ability to provide a high probability (approximately 90%) to reach a time to signal within 15 months of the last study for a vaccine with an assumed 65% VE or higher. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender.

Of the total sample size, a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be <40 years of age. Details on the possible blinded sample-size reassessment will be described in the statistical analysis plan (SAP).

INTERVENTION GROUPS AND DURATION

Participants will be vaccinated at the study site according to the schedules detailed above:

- Ad26.COV2.S supplied at a concentration of 1×10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp
- Placebo: 0.9% sodium chloride (NaCl) solution

For blinding purposes, all participants will receive a vaccination at Day 1 and at Day 57, using the same volume (ie, 0.5 mL).

EFFICACY EVALUATIONS

Identification and molecular confirmation of SARS-CoV-2 infection and symptomatic COVID-19 will be performed throughout the study.

The occurrence of COVID-19-related hospitalization and COVID-19-related complications (such as but not limited to hyperinflammatory syndrome, pneumonia, neurological or vascular complications, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death)[a] will be monitored throughout the study.

For the primary objective, all moderate to severe/critical COVID-19 cases will be considered.

[a] World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance, 13 March 2020. https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. Accessed 12 May 2020.

As a secondary objective, VE in the prevention of asymptomatic SARS-CoV-2 infection and mild COVID-19 will be analyzed.

An immunologic test for SARS-CoV-2 seroconversion (ELISA and/or SARS-CoV-2 immunoglobulin assay) based on SARS-CoV-2 N protein, will be performed to identify cases of asymptomatic infection. This assay will be performed on samples obtained at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination.

IMMUNOGENICITY EVALUATIONS

Blood will be collected from all non-Immunogenicity Subset participants for humoral immunogenicity assessments at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination.

For a total of approximately 400 participants in the Immunogenicity Subset (ie, 400 participants at sites with access to appropriate processing facilities), blood will be collected for analysis of humoral immune responses before each vaccination, 28 days after the 1st vaccination and 14 days, 6 months, 1 year, 18 months, and 2 years after the 2nd vaccination

For participants with suspected or confirmed COVID-19 (ie, meeting prespecified criteria on COVID-19 Day 1-2 and Day 3-5 and/or a SARS-CoV-2 positive sample on COVID-19 Days 1-2 or 3-5), blood will be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 for immunogenicity assessments, including the assays summarized in the table below.

Immunogenicity Assays

Humoral Assays	**Purpose**
Supportive of Secondary Objectives	
SARS-CoV-2 binding antibodies to S protein (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
SARS-CoV-2 seroconversion based on antibodies to N protein (ELISA and/or SARS-CoV-2 Immunoglobulin assay)	Analysis of antibodies binding to SARS-CoV-2 N protein
Supportive of Exploratory Objectives	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus, and/or pseudovirion expressing S protein
SARS-CoV-2 binding antibodies to S protein (MSD)	Analysis of antibodies binding to SARS-CoV-2 S protein (different than the assays supportive of the secondary objectives) and the receptor-binding domain (RBD) of SARS-CoV-2 S protein
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, avidity, crystallizable fragment (Fc)-mediated viral clearance, Fc characteristics, immunoglobulin (Ig) subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire
Adenovirus neutralization (VNA)	Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector
Binding antibodies to other coronaviruses (MSD)	Analysis of antibodies binding to coronaviruses other than SARS-CoV-2

Ad26 = adenovirus type 26; ELISA = enzyme-linked immunosorbent assay; Fc = crystallizable fragment; Ig(G) = immunoglobulin (G); MSD = Meso Scale Discovery; N = nucleocapsid; RBD = receptor-binding domain; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay.

In areas where seroprevalence is predicted to be high, a screening serologic test for past or current infection with SARS-CoV-2 may be performed (in a local laboratory), at the discretion of the sponsor, to restrict the proportion of seropositive participants in the study.

A serologic test for past or current infection with SARS-CoV-2 will be performed for all participants at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination. Samples for

the serologic tests will be sent to a central laboratory for testing[a]. Participants who test positive will be informed of the result by the study staff.

SAFETY EVALUATIONS

The first 1,000 participants will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 1,000 participants no acute reactions have been observed, the observation period at the study site may be reduced to at least 15 minutes after each vaccination for the remaining participants in the study.

For all participants:

- (S)AEs that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated informed consent form (ICF) is obtained until the end of the study/early withdrawal.
- Clinically relevant medical events not meeting the above criteria and occurring between signing of the ICF and moment of 1st vaccination will be collected on the Medical History electronic case report form (eCRF) page as pre-existing conditions.
- All SAEs and all AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of 1st vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.
- MAAEs are defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered medically-attended visits. New onset of chronic diseases will be collected as part of the MAAEs. MAAEs are to be reported for all participants from the moment of 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
- Special reporting situations, whether serious or non-serious, will be recorded for each vaccination from the time of vaccination until 28 days post-vaccination.
- All AEs will be followed until resolution or until clinically stable.

For participants in the Safety Subset:

- Solicited AEs, collected through an e-Diary, will be recorded from the time of each vaccination until 7 days post-vaccination. If these solicited signs and symptoms are not resolved by that time, the participant will continue to complete the e-Diary until Day 29 post-vaccination or until they are resolved, whichever comes first.
- All other unsolicited AEs, whether serious or non-serious, will be recorded from the time of each vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

[a] Vaccination with Ad26.COV2.S may interfere with some serologic assays utilized at local community health clinics/commercial laboratories, by seeking and identifying the spike protein in the vaccine and rendering a false positive result. For this reason, participants will be encouraged to not seek testing outside the study. If a participant requires testing outside of the protocol-mandated testing schedule, the site will guide them on the appropriate assay that identifies the viral nucleocapsid protein (and not the spike protein).

STATISTICAL METHODS

Sample Size Calculation

Efficacy (Total Sample Size)

The study target number of events (TNE) is determined using the following assumptions:

- a VE for molecularly confirmed, moderate to severe/critical SARS-CoV-2 infection of 65%.
- approximately 90% power to reject a null hypothesis of H0: VE≤30%.
- type 1 error rate $\alpha = 2.5\%$ to evaluate VE of the vaccine regimen (employing the sequential probability ratio test [SPRT] to perform a fully sequential design analysis; detailed in the methods section).
- a randomization ratio of 1:1 for active versus placebo.

Events are defined as first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition (see above) in the Per-protocol Efficacy population at least 14 days after the 2nd vaccination (Day 71) with study vaccine.

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 104, based on events in each active vaccination and placebo group, according to the primary endpoint case definition of moderate to severe/critical COVID-19.

If the primary hypothesis testing is successful, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%. The method to perform hypothesis testing of primary and secondary objectives preserving the FWER will be specified in the SAP. The FWER will be controlled at 2.5%.

The sample size is approximately 15,000/group (30,000 in total) and is determined based on an estimated annualized incidence rate of moderate to severe/critical COVID-19 of 1 to 4% at the start of the study to reach the requirements for efficacy evaluation within the targeted time frame.

The operating characteristics of the study design, statistical methods, study monitoring rules and efficacy evaluation specified in this protocol with the chosen event and sample sizes will be described in a separate modeling and simulation report and will be added to the SAP before the first participant is vaccinated.

Immunogenicity Correlates (Correlates Subset)

Correlates will be assessed in a subset where immune responses and transcriptome modifications are measured in all vaccine recipients who experience a SARS-CoV-2 event, and in random samples of vaccine recipients who have not been infected, in a 1:5 ratio. The goal of this case–control study is to assess correlates of risk of SARS-CoV-2 infection (and potential other secondary endpoints) in the vaccine group by comparing vaccine-induced immune responses and transcriptome modifications associated with COVID-19. Also, placebo participants will be included in this subset (placebo infected, seropositive [based on N-protein] non-infected and seronegative non-infected), if feasible.

Safety (Safety Subset)

Solicited and unsolicited AEs will be captured only in the Safety Subset, ie, approximately 6,000 participants (~3,000 from the active group, ~3,000 from the placebo group; and including at least 2,000 from the older age group [≥60 years of age] if feasible).

Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

- **Full Analysis Set (FAS):** All randomized participants with at least 1 documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment. Analyses of safety will be performed on the FAS. Vaccine efficacy analyses can be repeated using the FAS.
- **Safety Subset**: subset of the FAS for the analysis of solicited and unsolicited AEs.
- **Per-protocol Efficacy (PP) population[a]:** Participants in the FAS who receive 2 doses of study vaccine and who are seronegative at the time of 1st vaccination and at Day 71, and who have no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine. The PA of VE will be based on the PP population. The PP will be the main analysis population for efficacy analyses.
- **Per-protocol Immunogenicity (PPI) population[a]:** All randomized participants who receive 2 doses of study vaccine, including those who are part of the Immunogenicity Subset and for whom immunogenicity data are available, excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, for participants who experience a SARS-CoV-2 event (molecularly confirmed), samples taken after the event and samples taken outside protocol windows will not be taken into account in the assessment of the immunogenicity. The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants who are part of the Immunogenicity Subset for whom immunogenicity measures are available. Excluded samples might be taken into account as well in the sensitivity analysis. Analyses of vaccine immunogenicity and immune correlates of risk will be based on PPI.

The list of major protocol deviations to be excluded from the efficacy and/or immunogenicity analyses will be specified in the SAP and/or this list will be reported into protocol deviation dataset of the clinical database before database lock and unblinding.

Efficacy Analyses

The study will have 3 timepoints for efficacy analyses

1. The primary efficacy analyses, to evaluate the primary and secondary objectives of this study, will be performed as soon as the TNE has been reached, or earlier based on sequential monitoring. After the primary analysis, additional analyses to support health authority interactions may be planned, if deemed appropriate.
2. The final analysis will be performed when the last participant completes the visit 12 months after the last vaccination or discontinues earlier.
3. The end-of-study analysis will be performed when all participants have completed the visit 24 months after the last vaccination or discontinued earlier

Primary Endpoints

The study is designed to test the primary hypothesis of VE in the PP population: H0: VE ≤30% versus H1: VE >30%. The primary endpoint will evaluate the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition with onset at least 14 days after the 2nd vaccination (Day 71) with Ad26.COV2.S versus placebo, separately, in the PP population, including all events from both age groups, with and without comorbidities.

[a] If a participant would be vaccinated out of window due to a study pause, this will not by default be a reason for excluding this participant from the PP and PPI population. A sensitivity analysis might also be performed. Further details will be described in the SAP.

Participants included in the seronegative analysis set are those participants with a negative SARS-CoV-2 serology test result at baseline.

Evaluation of the Primary Endpoint

A fully sequential design with early stopping boundaries for efficacy based on the SPRT[24] will be used on the PP. The SPRT will control the type I error adjusting for the fully sequential approach. The decision rules for harm and non-efficacy are detailed in the protocol.

To that end, the boundaries are derived to achieve approximately 90% power to detect VE=65% using an alpha level of 2.5% against H0:VE≤30%.

To allow for durability assessment, sites and participants will continue the study and remain blinded until the final analysis.

A successful primary efficacy conclusion will require establishing the hypothesis H1: VE>30% for the primary endpoint.

To evaluate the primary null hypothesis: H0: VE ≤30% versus H1: VE >30% for the primary endpoint, the truncated sequential probability ratio test will be used based on accumulating event data. This boundary is set up using the fully sequential design and is derived in such a way to have approximately 90% power to detect a VE=65% using a one-sided alpha=0.025 against H0:VE≤30%. The specific boundaries will be detailed in the SAP.

The monitoring can start as soon as the following conditions are met:

1. A minimum of 6 COVID-19 cases for the ≥60 years age group
2. At least 20 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19

No interim evaluation will be done, until those conditions are fulfilled. Monitoring for efficacy will not start before the above conditions 1-2 and will occur at least once a week by the SSG of the IDMC until the prespecified boundaries have been crossed.

The minimum criteria that may trigger the primary analysis are listed below and the SAP will describe the additional criteria in detail:

1. a) An interim evaluation if both prespecified efficacy boundaries have been met OR if 104 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 are observed

   AND

   b) The above 2 conditions are met.

OR, alternatively,

2. If the prespecified non-efficacy has been met (evaluating events with start 14 days after the second vaccination) or when the harm boundary has been crossed. The decision rules for harm and non-efficacy are detailed in the body of the protocol.

If more than 104 primary endpoints are observed before the 2 conditions above are met, a single analysis will take place as soon as the conditions are met, using the full 2.5% one-sided significance level.

If the prespecified boundary is met, the SSG will inform the IDMC and if deemed appropriate by the IDMC, a meeting with the IDMC and Sponsor Committee will be set up to discuss the efficacy signal. Upon this meeting the Sponsor Committee can trigger internal decision procedures to initiate health authority interactions based on the outcome of the study.

If, in the event of waning incidence, it is clear that the necessary number of events cannot be collected with the available sample size within a reasonable timeframe, the PA may still be conducted based on the available data and prespecified decision rules. An operational rule that warrants for waning incidence will be specified in the SAP.

The primary efficacy analysis will pool data across populations (with and without comorbidities) to evaluate the primary and secondary objectives. In addition, these will be supplemented with a subgroup analysis for age and comorbidities employing a descriptive summary, including 95% confidence intervals to describe the VE in each subpopulation.

In addition, to assess potential time-effects of VE, the Kaplan-Meier method will be used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate cumulative VE over time, defined as [(1 minus ratio (vaccine/placebo) of cumulative incidence by time t) ×100%].

Secondary Endpoints

All secondary endpoint analyses will occur in the PP analysis set, in seronegative participants unless otherwise indicated.

The multiple testing strategy and the timing of the hypothesis testing to evaluate the secondary objectives will be detailed in the SAP separately.

Immunogenicity Analyses

No formal statistical testing of the immunogenicity data is planned. All immunogenicity analyses will be performed on the PPI set. Key tables might be repeated for the FAS (including samples that are excluded from the PPI analysis).

Safety Analyses

No formal statistical testing of safety data is planned. Safety data by vaccination group and based on the FAS will be analyzed descriptively. The analysis of solicited and unsolicited AEs will be restricted to a subset of the FAS (ie, the Safety Subset). For SAEs and MAAEs the full FAS is considered. New onset of chronic diseases will be collected as part of the MAAEs.

Interim Analyses and Committees

The study will be formally monitored by an IDMC. In general, the IDMC will monitor safety data on a regular basis to ensure the continuing safety of the participants. The IDMC will review unblinded data.

The IDMC will review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing studies) from participants enrolled in Stage 1, before enrollment of participants in Stage 2. Enrollment will not be paused during other safety reviews. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

Continuous monitoring for vaccine-associated enhanced disease will be performed through the SSG who will look at each of the diagnosed FAS COVID-19 events. Vaccine harm monitoring will be performed for severe/critical COVID-19/death endpoint based on the FAS. As these events will be monitored in real-time, and, after each confirmed respective case, the SSG will assess if a stopping boundary is reached. Specifically, monitoring for a higher rate of severe/critical disease or death in the vaccine group compared to the placebo group starts at the 5^{th} event and at each additional event until the harm boundary is reached or until the primary analysis is triggered. If the stopping boundary is met, then the SSG immediately informs the Chair of the IDMC through secure communication procedures. At this point the IDMC will convene and provide a recommendation to the Sponsor Committee. As such, the potential harm monitoring is in

real-time, resulting in the earliest indication of harm possible as soon as data come in. In addition, the IDMC will formally monitor the SARS-CoV-2 events to conclude both non-efficacy and efficacy. The IDMC will evaluate in an unblinded fashion whether superiority is established for the primary endpoint or whether non-efficacy is shown based on a report provided by the SSG, when the prespecified boundaries have been crossed.

The study will also be monitored for operational non-efficacy to evaluate whether enough events to perform the PA can be collected within reasonable time. For that purpose, a monitoring rule will be set up to assess the probability that the minimal needed target number of primary endpoint events to be able to perform the PA in the PP set will be reached. Two versions of the non-efficacy monitoring report will be generated. A report provided to the IDMC will contain unblinded events and a report provided to the Sponsor Committee will contain blinded events. While it is the primary responsibility of the Sponsor Committee to make decisions regarding study operations and modifications based on monitoring of study vaccine-blinded primary events from the study, the IDMC can evaluate the progress towards primary endpoint targets in the context of the study vaccine-unblinded data, and based on this review may recommend to the Sponsor Committee to complete the study early due to reaching a boundary for efficacy or non-efficacy to assess VE.

The monitoring rules will be detailed in the IDMC charter, with the statistical details in the SAP.

The SAP will describe the planned analyses in greater detail.

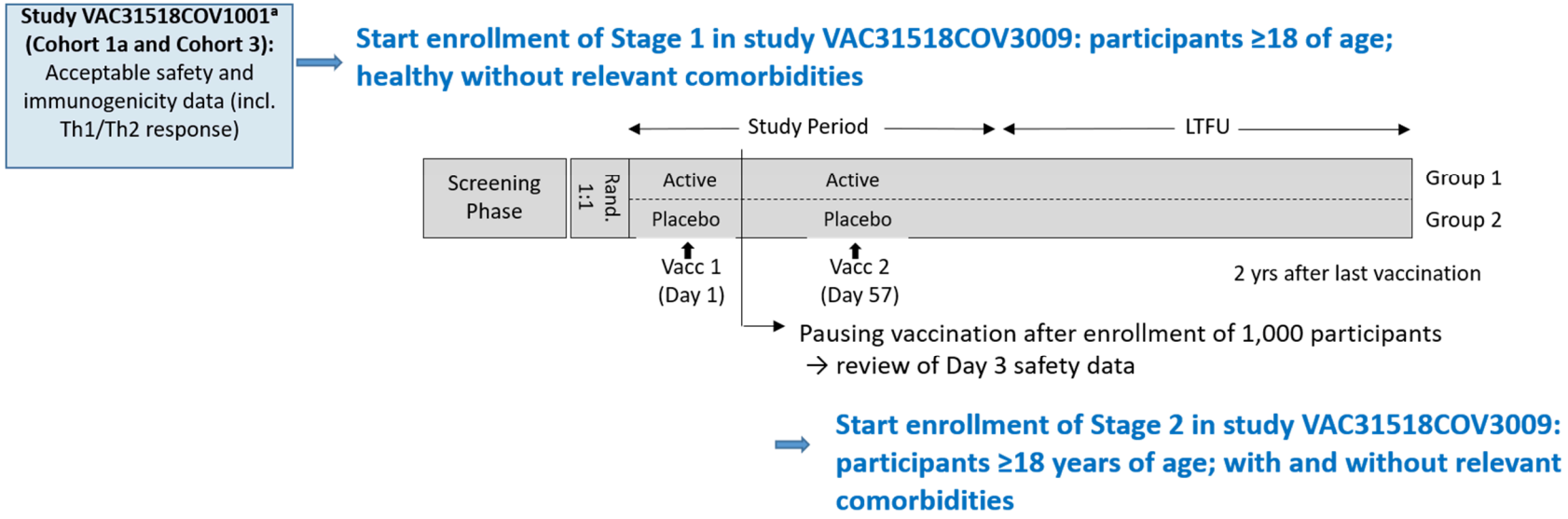
Unblinding due to availability of an authorized/licensed COVID-19 vaccine

Investigators may receive requests to unblind study participants who become eligible to receive an authorized/licensed COVID-19 vaccine if/when these become available. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorized/licensed vaccine according to local immunization guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures. The reason for the unblinding request should be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see body of the protocol for more details).

When unblinding, if it is determined that the participant received the Ad26COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. In the event the participant is unblinded, no further study vaccination will be permitted. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the Schedules of Activities to the extent that they permit. Safety, efficacy, and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, including participants in the safety subset, if applicable and feasible. All data will be analyzed separately from the point of unblinding, for safety, efficacy, and immunogenicity analysis, as described in the Statistical Analysis Plan.

1.2. Schema

Figure 1: Schematic Overview of Study VAC31518COV3009



Active = Ad26.COV2.S; incl. = including; LTFU = long-term follow-up; rand. = randomization; Th = T-helper cell type 1/2.

[a] Available safety data from all ongoing studies with Ad26.COV2.S will be taken into account.

A screening phase of up to 28 days is included, however, screening may also be performed prior to randomization on the day of vaccination.

The enrollment for Stage 1 and Stage 2 will be staggered. In both stages, participants will be enrolled in 1 of the 2 age-dependent subgroups (≥18 years to <60 years of age or ≥60 years of age). Once Stage 2 is initiated, participants with and without relevant comorbidities can be recruited. It is intended that a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be ≥18 to <40 years of age. The analysis of the data will not be staggered: the primary analysis will be based on pooled data from both stages of the study.

Refer to Section 2.1 for details on initiation of study VAC31518COV3009 based on data from study VAC31518COV1001.

Refer to the IB for details about the VAC31518COV1001 study.[33,34]

Refer to Section 5.2 for details on the relevant comorbidities.

1.3. Schedules of Activities

1.3.1. All Participants

Phase	Screening[a]	Study Period							Long-term Follow-up		
Visit #[b]	1	2	3	4	5	6[c]	7	8	9	10	Exit[d]
Visit Timing		Vac 1	Vac 1 + 28 d	Vac 2	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 24 w	Vac 2 +52 w	Vac 2 +78 w	Vac 2 +104 w	
Visit Day/Week	Day -28 to 1	Day 1	Day 29*	Day 57	Day 71*	Day 85*	Week 32* (6m post Vac 2)	Week 60* (1y post Vac 2)	Week 86* (18m post Vac 2)	Week 112* (2y post Vac2)	
Visit Window			±3 d	±14 d	±3 d	±3 d	±21 d	±21 d	±28 d	±28 d	
Visit Type	Screening	Vaccine 1	Safety and Immuno	Vaccine 2	Safety and Immuno	Safety	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Early Exit
Informed consent[e]	●										
Inclusion/exclusion criteria	●	●[#,f]									
Demographics	●										
Risk factor assessment[g]		●[#]			●		●	●			
Optional consent to access medical data in US only						●[h]					
Relevant medical history[i]/prestudy therapies[j]	●	●[#]									
Body weight and height	●										
Vital signs[j]	●										
Body temperature[k]	●	●[#]	●	●[#]	●	●	●	●	●	●	●[l]
Urine pregnancy test[m]	●	●[#]		●[#]							
Pulse oximetry		●[#]									
Randomization		●[#]									
Nasal sample collection for SARS-CoV-2 testing[n]		●[#]									
Blood sample collection for screening serological test for anti-SARS-CoV-2 antibody[o]	●										
MRU questionnaire (baseline version)[o]		●[#]									
Pre-vaccination symptoms[q]		●[#]		●[#]							
eCOA training and set-up[r]		●[#]									
Distribution of thermometer		●[#]									
Distribution of pulse oximeter[s]		●[#]									
Distribution of MA-COV form[t]		●[#]									
Training and distribution: nasal swab kit and saliva recipients		●[#]									

Phase	Screening[a]	Study Period							Long-term Follow-up		
Visit #[b]	**1**	**2**	**3**	**4**	**5**	**6[c]**	**7**	**8**	**9**	**10**	**Exit[d]**
Visit Timing		**Vac 1**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 14 d**	**Vac 2 + 28 d**	**Vac 2 + 24 w**	**Vac 2 +52 w**	**Vac 2 +78 w**	**Vac 2 +104 w**	
Visit Day/Week	**Day -28 to 1**	**Day 1**	**Day 29***	**Day 57**	**Day 71***	**Day 85***	**Week 32*** (6m post Vac 2)	**Week 60*** (1y post Vac 2)	**Week 86*** (18m post Vac 2)	**Week 112*** (2y post Vac2)	
Visit Window			**±3 d**	**±14 d**	**±3 d**	**±3 d**	**±21 d**	**±21 d**	**±28 d**	**±28 d**	
Visit Type	**Screening**	**Vaccine 1**	**Safety and Immuno**	**Vaccine 2**	**Safety and Immuno**	**Safety**	**Safety and Immuno**	**Safety and Immuno**	**Safety and Immuno**	**Safety and Immuno**	**Early Exit**
Symptoms of Infection with Coronavirus-19 (SIC), including body temperature measured by the participant (ePROs to be completed by the participant in the eCOA)[u]		●[#]									
Vaccination		●		●							
Post-vaccination observation[v]		●		●							
(Suspected) COVID-19 surveillance (symptom check)[w]		*Continuous*									
MAAE recording[x]		*Continuous*									
(S)AE recording[y]		*Continuous*									
Concomitant therapies[z]		*Continuous*									
Humoral immunogenicity (serum), mL (non-Immunogenicity Subset Participants)[aa]		●[#]10			●10		●10	●10			●10[bb]
IMMUNOGENICITY SUBSET ONLY											
Humoral immunogenicity (serum), mL[cc]		●[#]15	●15	●[#]15	●15		●15	●15	●15	●15	●15[bb]
SAFETY SUBSET ONLY											
Solicited AE recording[dd]		*Cont+7d*		*Cont+7 d*							●[ff]
Unsolicited AE recording[ee]		*Cont +28 d*		*Cont +28 d*							●[ff]
Ruler training and distribution of ruler[gg]		●									
Participant e-Diary review			●			●					
Approx. blood draw per visit, mL: 400 participants (Immunogenicity Subset) [Other participants]		15.0 [10.0]	15 [0.0]	15 [0.0]	15 [10.0]	0.0 [0.0]	15 [10.0]	15 [10.0]	15 [0.0]	15 [0.0]	15 [10.0]
Approx. cumulative blood draw, mL: 400 participants (Immunogenicity Subset) [Other participants]		15.0 [10.0]	30.0 [10.0]	45.0 [10.0]	60.0 [20.0]	60.0 [20.0]	75.0 [30.0]	90.0 [40.0]	105.0 [40.0]	120.0 [40.0]	

[#] pre-vaccination

*These visits are to be scheduled relative to the actual day of the previous vaccination

a. Screening will be performed within 28 days prior to the 1st study vaccination or on the day of vaccination. If screening is performed on the day of vaccination (recommended), Visit 1 and Visit 2 will coincide on Day 1. In that case, assessments should only be done once. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.
b. If allowed by local regulations, study visits may take place at the participant's home or other location in the event of ongoing SARS-CoV-2 transmission in the area of the participant. If possible and allowed per local regulation, visits can be performed by a phone call or a telemedicine contact. Except for the screening and vaccination visits, assessments scheduled for the other visits may also be performed by a trained health care professional (HCP), if allowed per local regulations.
c. Visit 6 is only applicable for participants in the Safety Subset.
d. For those participants who are unable to continue participation in the study up to Visit 10, but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent from participation in the study will be offered an optional visit for safety follow-up. This includes the safety assessments of the early exit visit (no blood sampling for immunogenicity).
e. Signing of the ICF should be done before any study-related procedure. The ICF can be signed remotely prior to the Screening Visit. Downloading of an application to the participant's eDevice, to access materials for enrollment and study information, is not considered a study-related procedure.
f. Check clinical status again before 1st study vaccination.
g. If allowed by local regulations and if the participant consents, he/she will be interviewed on characteristics related to his/her current work situation, living situation, and community interactions on Day 1 (See Appendix 12) and, at other timepoints, on changes compared to Day 1. These data will be used for risk factor analyses.
h. For US participants only, at Day 29 or any time thereafter, the participant will be asked for optional consent to allow access to their medical data (electronic health records, claims, laboratory data from other care settings) from 5 years prior to study enrollment until 5 years after study completion utilizing tokenization and matching procedures (see Section 4.2 and Section 8.7) Participants will be informed that consent can be withdrawn at any given time. The sponsor will then remove the token generated and any associated linked real-world data (Section 4.2.1)
i. Only relevant medical history is to be collected, in particular: congenital abnormalities, history of cancer, history of immunodeficiency or conditions treated with immunomodulators, major psychiatric illness, major cardiovascular or lung diseases, history of an allergy to vaccination, ongoing comorbidities, history of any comorbidity known to be associated with an increased risk of progression to severe COVID-19, and history of hepatitis B or hepatitis C infection.
Participants with stable/well-controlled HIV infection are allowed to enroll in the study (see Section 5.1). These participants will be encouraged to have HIV RNA viral load and CD4 cell count assessed at least twice a year and to provide these data for inclusion in the eCRF.
j. Prestudy therapies are only to be recorded for participants with relevant comorbidities and participants aged ≥60 years. For these participants, all prestudy therapies (excluding vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, and exercise regimens) administered up to 30 days before the 1st vaccination must be recorded at screening.
Vital signs may be measured at the discretion of the investigator. Under special circumstances such as high altitude, the investigator should assess baseline respiratory rate and other vital signs, as appropriate.
k. Body temperature will be measured preferably via the oral route, or in accordance with the local standard of care.
l. If within 7 days of the vaccination.
m. For participants of childbearing potential only.
n. Diagnostic molecular RT-PCR test for SARS-CoV-2 infection (from nasal swab collected prior to vaccination on Day 1) will be performed at a central laboratory on a retrospective basis. These baseline results will not be available in real time, and thus cannot be used to inform participants at time of enrollment.
o. In areas where seroprevalence is predicted to be high, a screening serologic test for past or current infection with SARS-CoV-2 may be performed (in a local laboratory) at the discretion of the sponsor to restrict the proportion of seropositive participants in the study. This procedure should not be performed unless the site is instructed to implement the test by the Sponsor. The decision will be based on Sponsor-assessed local seroprevalence.
p. MRU over the last 3 months before the 1st vaccination will be collected by interview with the participant and recorded in the eCRF.

q. Investigator must check for acute illness or body temperature ≥38.0°C/100.4°F at the time of vaccination. If any of these events occur within 24 hours prior to the planned vaccination, the vaccination can be rescheduled as long as this is within the allowed window. If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

r. Participants will complete the eCOA using an application on their own eDevice (smartphone or tablet) if their device is compatible with the application or using the web portal.
All eCOA assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses.
If a participant is unable to complete the eCOA, a study staff member or the participant's caregiver can collect information on the participant's behalf as detailed in Section 8.1.2.

s. All participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.2).

t. The Medically-attended -COV form (Appendix 8) will be provided to the participant at the 1st vaccination visit and should be completed by the medical care provider or the study site personnel during medical visits for COVID-19 or COVID-19 complications.

u. The SIC questionnaire asks the participant if he/she had any of the prespecified signs or symptoms (see Appendix 6) during the past 24 hours (including highest temperature in the last 24 hours), and (when applicable) to rate the severity.

v. The first 1,000 participants will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 1,000 participants no acute reactions have been observed, the observation period at the study site may be reduced to at least 15 minutes after each vaccination for the remaining participants in the study. For participants in the Safety Subset, any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, and concomitant therapies will be documented by study-site personnel following this observation period. Participants will be allowed to leave the study site after it is documented that the post-vaccination observation period is complete.

w. Until 1 year after the 2nd vaccination, each participant will be asked at least twice a week, through the eCOA, if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. As of 1 year after the 2nd vaccination, until the end of the 2-year follow-up period, the frequency of this (suspected) COVID-19 surveillance (symptom check) through the eCOA will decrease to once every 2 weeks. Sites should reach out to a participant if the participant fails to complete the surveillance question upon any of these reminders. The questionnaire will be accessible on the eCOA platform in between scheduled reminders and participants will be encouraged to answer the surveillance question in the eCOA as soon as possible after the onset of COVID-19-like symptoms. Every effort will be made to document the status of all participants that are lost to follow-up due to not completing the eCOA and for whom hospitalization has not been recorded.
If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.2 and Section 8.1.2.
Enrolled participants will be counselled on SARS-COV-2 infection prevention each time that they have a contact with site staff, in line with local guidelines.
At the time of study entry, each participant will need to indicate to the study site, in case they would get infected with SARS-CoV-2, the identity and location of their routine medical care physician and/or facility and the identity and location of where they would obtain emergency care and hospitalization if necessary. If this information is not available, a plan for where such care could be obtained should be developed. If a participant should have COVID-19 and their symptoms deteriorate, they will be instructed to go to the HCP or hospital that has been identified in advance.

x. MAAEs are to be reported for all participants from the moment of the 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study. New onset of chronic diseases will be collected as part of the MAAEs.

y. All (S)AEs related to study procedures or non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of the 1st vaccination until completion of the participant's last study-related procedure. Special reporting situations, whether serious or non-serious, are to be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. Participants will be reminded once a month to contact the study site in case of an SAE.

z. Refer to Section 6.8 for collection and recording of concomitant therapies associated with SAEs, solicited and unsolicited AEs, and MAAEs.

aa. Blood sample for humoral immunity at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination also include sample for sero-confirmation of SARS-CoV-2 infection.
bb. Blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw.
cc. Blood samples for humoral immunity at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination also include sample for sero-confirmation of SARS-CoV-2 infection. Samples will be collected for 400 participants at selected sites.
dd. A subset of participants (N=6,000; Safety Subset) will record solicited signs and symptoms (including body temperature) in an e-Diary via the eCOA from the time of each vaccination until 7 days post-vaccination. If these solicited signs and symptoms are not resolved by that time, the participant will continue to complete the e-Diary until Day 29 post-vaccination or until they are resolved, whichever comes first.
ee. All other unsolicited AEs will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. In order to perform the safety assessment after approximately 1,000 participants have been vaccinated in Stage 1, participants will be asked to reach out to the study site as soon as possible in case they experience a serious or severe adverse event.
ff. If within 28 days of the previous vaccination.
gg. A ruler to measure local injection site reactions will be distributed to each participant in the Safety Subset.

AE = adverse event; approx. = approximate; cont. = continuous; COVID-19 = coronavirus disease-2019; d = day(s); eCOA = electronic clinical outcome assessment; eCRF = electronic case report form; ePRO = electronic patient-reported outcome; ICF = informed consent form; MAAE = medically-attended adverse event; MRU = medical resource utilization; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19; vac = vaccination; w = week(s).

1.3.2. Participants With (Suspected) COVID-19

Timing relative to onset of signs and symptoms	COVID-19 Day 1-2	COVID-19 Day 3-5[a]		2-day cycle to be repeated[c,d,e]		COVID-19 Day 29 (±7 d)[f,g]
		Part 1	Part 2[b]	1st day of cycle	2nd day of cycle	
Location	**Home[h]**	**Site or Home[i,j]**	**Site or Home[i,j]**	**Home[j]**	**Home[j]**	**Site or Home[i,j]**
Participant to contact study site with any health concerns/participant notifies the site of becoming aware of a positive RT-PCR test	●					
Site to contact participant if COVID-19 signs or symptoms are recorded in eCOA	●					
Confirmation of suspected COVID-19 using prespecified criteria	●[k]	●[l]				
Nasal swab sample (collected by the participant at home)[m]	●[n]			●		
Nasal swab sample (collected by qualified study staff)		●[o]				
Saliva sample (collected by the participant)[p]			●		●	
Humoral immunity (serum), mL			●15			●15[q]
In case of signs and symptoms: Symptoms of Infection with Coronavirus-19 (SIC), including highest body temperature over the last 24 hours measured by the participant[r] (ePROs to be completed by the participant in the eCOA)	- - - - - - - - - - - - - - - - - *Daily* - - - - - - - - - - - - - - -					●[s]
In case of no signs or symptoms: (Suspected) COVID-19 surveillance (symptom check)	- - - - - - - - - - - - - *At least twice a week* - - - - - - - - - -					●
Risk factor assessment[t]			●			
Vital signs[u]		●				●
Targeted physical examination		●				●
Pulse oximetry by site staff		●				●
Pulse oximetry by the participant (ePRO to be completed by the participant in the eCOA)[v]	●[n]	- - - - - - - - - *3 times a day* - - - - - - - - -				
Medical history and description of COVID-19 episode (collected by interview with the participant)			●			●
MRU questionnaire (collected by interview with the participant)[w]			●			●
Capture medical information from medical visits for COVID-19 or COVID-19 complications (MA-COV form)[x]	- *Continuous* - - - - - - - - - - - - - - - - - -					
Concomitant therapies associated with COVID-19	- *Continuous* - - - - - - - - - - - - - - - - - -					
Study-site personnel to contact participant	- - - - - - - - - - - - - - *Weekly or more frequently* - - - - - - - - - - - - - -					

a. The visit at COVID-19 Day 3-5 should be scheduled 2 to 4 days after symptoms onset/positive RT-PCR test from outside the study.
b. Only applicable for participants that have signs and symptoms that meet the prespecified criteria for suspected COVID-19 (Section 8.1.1) on COVID-19 Day 3-5 or who have a positive test result for SARS-CoV-2 from COVID-19 Days 1-2 or 3-5 visits.

c. Participants should enter the 2-day cycles period, if they either have signs and symptoms that meet prespecified criteria for suspected COVID-19 at COVID-19 Day 3-5 or if any sample collected on COVID-19 Day 1-2 or 3-5 visits, is positive for SARS-CoV-2 .Participants should be encouraged by the site to collect nasal swabs and saliva samples as indicated in the Schedules of Activities. If the participant is unable or unwilling to collect all samples as requested, the participant should still complete the other COVID-19 assessments, including the visit at COVID-19 Day 29.
d. As soon as it is confirmed that both nasal swabs (collected on COVID-19 Day 1-2 and COVID-19 Day 3-5) are negative for SARS-CoV-2, the participant will not undertake any further COVID-19 procedures and will fall back to the default Schedules of Activities, until the end of the study/early withdrawal.
e. Participants should undertake the COVID-19 procedures until 14 days after symptom onset (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last. Resolution of a COVID-19 episode is defined as having 2 consecutive SARS-CoV-2 negative nasal swabs and 2 consecutive days with no COVID-19-related signs or symptoms. Once past COVID-19 Day 15, participants should stop the collection of nasal swabs and saliva samples as soon as 2 consecutive nasal samples are SARS-CoV-2 negative, but (if still symptomatic at that time) should continue completing the ePROs (including SIC, body temperature, and pulse oximetry) in the eCOA until 2 consecutive days with no COVID-19-related signs or symptoms.
f. Only applicable for participants that have at least 1 SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1-2 or Day 3-5.
g. The visit on COVID-19 Day 29 can be combined with a regular study visit if within the applicable visit windows.
h. The COVID-19 Day 1-2 nasal swab can be collected at the study site (or hospital or other location, if needed), if preferred by the participant.
i. All COVID-19 Day 3-5 and Day 29 assessments may be performed by a trained HCP at the participant's home, if allowed per local regulations.
j. If a participant has a positive test result for SARS-CoV-2 infection and/or depending on the medical status of the participant, the participant may be requested to remain at home and not visit the study site. If necessary, study-site personnel or a trained HCP will visit the participant at home (or at the hospital or other location, if needed), if allowed by local regulations. Under these circumstances, the participant will be contacted by the site at least once per week and the participant's medical care provider will be notified.
k. In case of COVID-19 like symptoms, based on the information collected through the SIC, the site will reach out to the participant at the latest on COVID-19 Day 2 (the day after the day of symptom onset) to assess whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.1). In case the participant would actively reach out to the site already on COVID-19 Day 1, the site should already make a first assessment on COVID-19 Day 1 to check whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.1). As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19.
l. In case of COVID-19 like symptoms, the site will interview the participant to assess whether the reported signs and symptoms still qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.1).
m. A nasal swab should be collected from the participant at home (using available material for home swabs provided by the study staff) as soon as the prespecified criteria for suspected COVID-19 are met and, in case of COVID-19 like symptoms, preferably on the day of symptom onset or the day thereafter (COVID-19 Day 1-2). The sample collected on COVID-19 Day 1-2 should be transferred to the study site, as arranged by the study site, as soon as possible after collection, preferably within 24 hours. Nasal swabs should also be collected once every 2 days until 14 days after symptoms onset (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last. These samples should be transferred to the study site, as arranged by the study site, within 3 days after collection. Details are provided in the laboratory manual. If the participant requires assistance, a trained HCP can help the participant to collect the nasal swabs. Depending on local practice, 2 samples may be collected.
n. The nasal swab should be collected and pulse oximetry should be started as soon as possible after it has been confirmed that the prespecified criteria for suspected COVID-19 (Section 8.1.1) are met.
o. For participants with suspected COVID-19, confirmation of SARS-CoV-2 infection by a central laboratory will be used for the analysis of the case definition. All nasal swabs will also be tested by a local laboratory for case management.

p. Saliva samples should be collected from the participant (using recipients provided by the study staff). The samples should be transferred to the study site, as arranged by the study site, within 3 days after collection. Details are provided in the laboratory manual. If the participant requires assistance, a trained HCP can help the participant to collect the saliva samples.
q. Blood sample for humoral immunity also includes sample for sero-confirmation of SARS-CoV-2 infection (antibody).
r. Participants should complete the (suspected) COVID-19 surveillance (symptom check). In case of COVID-19 like signs and symptoms, participants should be encouraged by the site to complete the SIC (Appendix 6) daily, preferably in the evening around the same time each day, starting on the first day they experience symptoms. Sites should remind the participant to complete the SIC, unless special circumstances occur such as hospitalization or ventilation, in which case the reason for not completing the SIC should be recorded by site staff in the clinical database.
If a participant is unable to complete the eCOA, a study staff member or the participant's caregiver can collect information on the participant's behalf as detailed in Section 8.1.2.
Participant should measure body temperature daily (oral route preferred, or in accordance with the local standard of care) and record the highest temperature in the last 24 hours.
s. If the participant does not have symptoms at that time, he/she will only need to complete the (suspected) COVID-19 surveillance (symptom check).
t. If allowed by local regulations and if the participant consents, he/she will be interviewed on characteristics related to their current work situation, living situation, and community interactions (See Appendix 12). These data will be used for risk factor analysis.
u. Includes measurement of vital signs (preferably supine systolic and diastolic blood pressure, heart rate, and respiratory rate [after at least 5 minutes rest] and body temperature). It is recommended that vital signs are measured before collection of nasal swabs and blood draws.
v. In case of COVID-19 like symptoms, the participant will be asked to measure blood oxygen saturation and pulse rate at home 3 times a day (preferably in the morning, at lunch time, and in the evening). The results will be recorded by the participant in the eCOA.
w. Data collected as part of the MRU will be recorded in the eCRF.
x. The MA-COV form (Appendix 8) will be provided to the participant at the vaccination visit and should be completed by the medical care provider or the study site personnel during medical visits for COVID-19 or COVID-19 complications.

Upon closure of the COVID-19 episode and procedures, all participants will fall back to the default Schedules of Activities, until the end of the study/early withdrawal. If the participant experiences new signs or symptoms suggesting possible COVID-19 at a later point in time, the participant would re-start the COVID-19 procedures from COVID-19 Day 1 onwards.

COVID-19 = coronavirus disease-2019; eCOA = electronic clinical outcome assessment; eCRF = electronic case report form; ePRO = electronic patient-reported outcome; MA-COV = medically-attended COVID-19; MRU = medical resource utilization; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19.

2. INTRODUCTION

Ad26.COV2.S (previously known as Ad26COVS1) is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein.

Unless clearly specified otherwise, this section presents information available at the time of the writing of the initial protocol, dated 22 August 2020. At that time, the Ad26.COV2.S Investigator's Brochure (IB) Edition 1.0 and its Addendum 1 were in place.[33,34]

Information about the disease, correlates of immunity, and safety issues concerning this new pandemic-causing virus are rapidly evolving. Therefore, it is critical to recognize that the approach outlined in this document might or will change as insights and discussions evolve.

For the most comprehensive nonclinical and clinical information regarding Ad26.COV2.S, refer to the latest version of the IB and its addenda (if applicable) for Ad26.COV2.S.

The term "study vaccine" throughout the protocol, refers to Ad26.COV2.S or placebo as defined in Section 6.1. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "participant" throughout the protocol refers to the common term "subject".

COVID-19 Vaccine and Considerations

Currently, there are no available vaccines for the prevention of coronavirus disease-2019 (COVID-19). The development of a safe and effective COVID-19 vaccine is considered critical to contain the current outbreak and help prevent future outbreaks.

Although the quantitative correlate of protection against SARS-CoV-2 infection has not yet been identified, neutralizing antibody responses against the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) S protein have been associated with protection against experimental SARS-CoV and MERS-CoV infection in nonclinical models.[17,69] Recent studies suggest that SARS-CoV-2 has several similarities to SARS-CoV based on the full-length genome phylogenetic analysis and the putatively similar cell entry mechanism and human cell receptor usage.[40,42,70] Therefore, a neutralizing antibody response against the SARS-CoV-2 S protein may also have a protective effect.

Adenoviral-vectored Vaccines

Recombinant, replication-incompetent adenoviral vectors are attractive candidates for expression of foreign genes for a number of reasons. The adenoviral genome is well characterized and comparatively easy to manipulate. Adenoviruses exhibit broad tropism, infecting a variety of dividing and non-dividing cells. The adenoviral vaccine (AdVac®) vector platform, developed by Crucell Holland B.V. (now Janssen Vaccines & Prevention B.V.) allows for high-yield production of replication-incompetent adenovirus vectors, eg, Ad26, with desired inserts. The adenovirus E1

region is deleted to render the vector replication-incompetent and create space for transgenes, with viral replication taking place in cells that complement for the E1 deletion in the virus genome. Ad26 has been selected as a potential vaccine vector because there is substantial nonclinical and clinical experience with Ad26-based vaccines that demonstrate their capacity to elicit strong humoral and cellular immune responses and their acceptable safety profile, irrespective of the antigen transgene (see also Section 2.3.1).

The immunogenicity profile of adenoviral vectors is illustrated by data obtained following the immunization of adults with Ad26-vectored human immunodeficiency virus (HIV) vaccines (Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV), an Ad26-vectored Ebola virus vaccine (Ad26.ZEBOV), Ad26-vectored respiratory syncytial virus (RSV) vaccines (Ad26.RSV.FA2 and Ad26.RSV.preF), an Ad26-vectored Zika virus vaccine (Ad26.ZIKV.001), and an Ad26-vectored malaria vaccine (Ad26.CS.01). Antigen-specific antibody responses are observed in almost all participants after 1 dose, in both naïve and pre-immune individuals (RSV). These antibodies may persist for a year or more (RSV) after a single-dose in pre-immune participants. They have functional properties of neutralization (RSV, Zika), crystallizable fragment (Fc)-mediated antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (HIV, malaria). Furthermore, these data support an immunogenicity profile with emphasis on T-helper cell type 1 (Th1) responses and demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in $CD4^+$ and $CD8^+$ T cells.[3,35,45]

Ad26.COV2.S Candidate Vaccine

The aim of the COVID-19 vaccine clinical development program is to develop a safe and effective vaccine for the prevention of COVID-19. The candidate vaccine to be assessed in this study is Ad26.COV2.S, which is a recombinant, replication-incompetent Ad26 encoding a prefusion stabilized variant of the SARS-CoV-2 S protein. The parental S protein sequence was derived from a SARS-CoV-2 clinical isolate (Wuhan, 2019; whole genome sequence NC_045512). The selection of antigen was based on previous work on the SARS-CoV and MERS-CoV candidate vaccines.[17,27,46] The S protein is the major surface protein on coronaviruses and is responsible for binding to the host cell receptor and mediating the fusion of host and viral membranes, thereby facilitating virus entry into the cell.[72]

SARS-CoV-2 Virology and COVID-19 Disease Burden

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[20,65] It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019.[41] Early epidemiological investigations suggested that the majority of early cases were linked to a seafood market, with patients infected through zoonotic or environmental exposure, followed by the subsequent spread of infection by human-to-human transmission among close contacts.[41] However, there is some controversy about the initial origin of the virus.[21] Genomic sequencing was performed on bronchoalveolar lavage fluid samples collected from patients with viral pneumonia admitted to hospitals in Wuhan, which identified a novel RNA virus from the family Coronaviridae.[42,65] Phylogenetic analysis of the complete viral genome revealed that the virus, SARS-CoV-2, is part of the subgenus Sarbecovirus

of the genus Betacoronavirus, and is most closely related (approximately 88% identity) to a group of SARS-CoV-like coronaviruses previously sampled from bats in China.[42]

SARS-CoV-2 has spread rapidly and globally since its emergence. The World Health Organization (WHO) declared that the outbreak constituted a public health emergency of international concern on 30 January 2020, and declared the outbreak to be a pandemic on 11 March 2020.[62,63] As of 1 June 2020, approximately 6,680,000 cases of COVID-19 and approximately 375,000 COVID-19-related deaths have been reported.[36]

Symptoms of infection may appear from 2 to 14 days following exposure, with the clinical manifestations ranging from mild symptoms to severe illness or death.[11] Severe clinical presentations have been reported in as many as 20% to 25% of laboratory-confirmed cases.[26] In a study of 99 patients in a single center in Wuhan with SARS-CoV-2 infection confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR), the most commonly reported clinical manifestations were fever (83%), cough (82%), shortness of breath (31%), and muscle aches (11%).[16] In chest X-rays and computed tomographic (CT) scans, 75% of patients showed bilateral pneumonia and 14% of patients showed diffuse mottling and ground-glass opacities. In a further study of 138 patients with novel coronavirus-induced pneumonia in a single center in Wuhan, common symptoms included fever (98.6%), fatigue (69.6%), and dry cough (59.4%).[55] Lymphopenia occurred in 70.3% of patients, and chest CT scans showed bilateral patchy shadows or ground-glass opacities in the lungs of all patients. Thirty-six patients (26%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome, arrhythmia, and shock. Subsequent United States (US) Centers for Disease Control and Prevention (CDC) descriptions of COVID-19 clinical case definitions[11] and Janssen-sponsored interviews with COVID-19-experienced clinicians have included signs and symptoms of respiratory distress such as blue lips, extreme shortness of breath and dyspnea, persistent cough, deep vein thrombosis (DVT), Kawasaki-like disease, discoloration of feet and toes, chills, shaking chills, loss of sense of taste and smell, signs of stroke, disorientation, inability to respond or understand verbal communication, among others.

At present, it appears that individuals aged ≥65 years, especially those with comorbid diseases, are subject to the highest incidence of morbidity and mortality.[29] In contrast, a study of 2,143 children aged <18 years in China with laboratory-confirmed (34.1%) or suspected (65.9%) COVID-19 indicated that the clinical manifestations of the disease may be less severe in children than adults, with approximately 94% of cases being asymptomatic, mild, or moderate.[23] However, young children, particularly infants, were susceptible to severe disease, with the highest proportion of severe and critical cases by age group reported for children aged <1 year (10.6% of cases in this age group). A study of 149,082 COVID-19 cases reported in the US was consistent with these findings.[14] Only 1.7% of these cases occurred in persons aged <18 years although this age group accounts for 22% of the US population. Furthermore, relatively few pediatric COVID-19 cases were hospitalized, indicating that COVID-19 might have a mild course among younger patients. Hospitalization was most common among pediatric patients aged <1 year and those with underlying conditions. Recent (April-May 2020) reports describe several cases of multisystem inflammatory syndrome (MIS) in children with Kawasaki disease-like features (ie, fever,

laboratory markers of inflammation, severe illness requiring hospitalization, multisystem organ involvement). Most of these children had tested positive for current or recent SARS-CoV-2 infection or were linked to a COVID-19 case. It is currently unknown if MIS is specific to children or if it may also occur in adults.[10,60]

The identification of SARS-CoV-2 follows the emergence of 2 other novel betacoronaviruses capable of causing severe human disease over the past 18 years: SARS-CoV and MERS-CoV, which have nucleotide sequence identity with SARS-CoV-2 of approximately 79% and 50%, respectively.[42] The first known cases of severe acute respiratory syndrome (SARS) occurred in Southern China in November 2002.[64] The etiological agent, SARS-CoV, is believed to be an animal virus that crossed the species barrier to humans followed by human-to-human transmission, leading to SARS cases in >25 countries. The MERS-CoV was isolated from a patient in Saudi Arabia who died of severe pneumonia and multi-organ failure in June 2012.[72] MERS-CoV is considered to be a zoonotic virus capable of nonsustained human-to-human transmission. Since 2012, sporadic cases and community and health-care-associated clusters of infected individuals have been reported in the Middle East.

Patients with SARS or MERS present with various clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory disease with extrapulmonary manifestations.[15,72] Both diseases have predominantly respiratory manifestations, but extrapulmonary features may occur in severe cases. By July 2003, the international spread of SARS-CoV resulted in 8,098 SARS cases and 774 deaths (case- fatality rate: 10%) with substantial social, economic and health service disruption in some affected countries.[15,64] The case-fatality rate of MERS-CoV infections is estimated to be 35%.[15]

It is not known if SARS-CoV-2 will remain as a worldwide pandemic. It is also not known if immunity is acquired after symptomatic or asymptomatic SARS-CoV-2 infection and how long it might last. Currently, the only preventive measures that have been employed with some success have been social distancing and quarantine after contact tracing and testing. Test and treat approaches await an effective proven safe therapy that can be implemented on a mass scale. It is generally believed that an effective vaccine will be 1 of the most important tools to help control this highly contagious respiratory virus.

2.1. Study Rationale

The sponsor is developing a COVID-19 vaccine based on a human replication-incompetent Ad26 vector encoding the SARS-CoV-2 S protein. The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate coronavirus vaccines against SARS-CoV (2003 outbreak), and the common conclusion that has emerged from the evaluation of several different vaccines is that the viral S protein is the only significant target for neutralizing antibodies[8,53,68,71] and the only viral protein that can elicit protective immunity in animal models.[5,6,9,52,66] Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen.

Even though a single-dose regimen in study VAC31518COV1001 showed good immunogenicity that may already protect against COVID-19, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in a higher and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study. The single dose regimen will be further evaluated in study VAC31518COV3001.

Vaccine-associated enhanced disease has been described in some animal models for SARS and MERS in which candidate vaccines induced a Th2 biased immune response,[1,7,22,31,32] but proof of human SARS- or MERS-vaccine-associated enhanced disease does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. The Ad26 vector was chosen due to its ability to induce humoral and strong cellular responses with a Th1 immune phenotype.[2,4,19,45,48,49,51,59,61,67] This type 1 polarity of the immune response is thought to minimize the risk of enhanced disease after SARS-CoV-2 infection.

Study VAC31518COV3009 will include participants ≥18 years of age, with and without comorbidities that are associated with increased risk of progression to severe COVID-19. Enrollment of participants in these 2 categories will be initiated in a staggered manner, as described below.

Stage 1: the study will start by enrolling approximately 1,000 participants in 2 age-dependent subgroups (≥18 years to <60 years of age and ≥60 years of age) without comorbidities that are associated with increased risk of progression to severe COVID-19 (including approximately 500 Ad26.COV2.S recipients and approximately 500 placebo recipients), then vaccination will be paused to allow the Independent Data Monitoring Committee(IDMC) to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing studies).

Stage 2: if no safety concerns are identified in Stage 1, enrollment will proceed, expanding enrollment to participants with or without comorbidities that are associated with increased risk of progression to severe COVID-19 in 2 age-dependent subgroups (≥18 years to <60 years of age and ≥60 years of age) (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).

The total sample size for the study (Stages 1 and 2) will be 30,000 participants. It is intended that a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be ≥18 to <40 years of age. This sample size range is determined based on an estimated annualized COVID-19 incidence of 1% to 4% at study start and the number of COVID-19 cases needed to reach the requirements for efficacy evaluation within the targeted time frames. The actual sample size for the study, 30,000 participants, will be selected at the operational cut-off date before initiation of the study, based on estimated incidence rates for the targeted study region and population at that time. Enrollment may be stopped if the primary endpoint is reached.

This sample size takes into consideration the uncertainty of the epidemiological situation in combination with the ability to provide a high probability (approximately 90%) to reach a time to signal within 15 months of the last study for a vaccine with an assumed 65% VE or higher. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender. Details on the

possible blinded sample-size reassessment will be described in the Statistical Analysis Plan (SAP). Refer to Section 9.2.1 for details about the sample size determination.

2.2. Background

Nonclinical Pharmacology

Nonclinical studies were performed to test the immunogenicity of different vaccine candidates, leading to the selection of the current vaccine for this development program. In addition, VE of Ad26.COV2-S has been shown in Syrian hamsters and NHP. Details are provided in the IB.[33,34]

Nonclinical Safety

Biodistribution

To assess distribution, persistence, and clearance of the Ad26 viral vector platform, intramuscular (IM) biodistribution studies have been conducted in rabbits using an Ad26-based HIV vaccine, Ad26.ENVA.01, and an Ad26-based RSV vaccine, Ad26.RSV.preF. In the available biodistribution studies, the Ad26 vector did not widely distribute following IM administration in rabbits. Ad26 vector deoxyribonucleic acid (DNA) was primarily detected at the site of injection, draining lymph nodes and (to a lesser extent) the spleen. Clearance of the Ad26 vector from the tissues was observed. Both Ad26 vectors showed a comparable biodistribution despite carrying different antigen transgenes. These data further indicate that the Ad26 vector does not replicate and/or persist in the tissues following IM injection. These platform data are considered sufficient to inform on the biodistribution profile of Ad26.COV2.S for which the same Ad26 vector backbone is used.

Toxicology

The sponsor has significant nonclinical experience with Ad26-vectored vaccines using various transgenes encoding HIV, RSV, Ebola virus, filovirus, human papilloma virus, Zika, influenza (universal flu [Uniflu]), and malaria antigens. To date, more than 10 Good Laboratory Practice (GLP) combined repeated dose toxicology and local tolerance studies have been performed in rabbits (and 1 study in rats), testing the nonclinical safety of various homologous and heterologous regimens with Ad26-based vaccines at full human doses up to 1.2×10^{11} vp. No adverse effects have been observed in these studies. The vaccine-related effects observed were similar across studies, considered to be reflective of a physiological response to the vaccines administered, and seem to be independent of the antigen transgene. Overall, there were no safety signals detected in any of the available GLP toxicology studies with Ad26-based vaccines up to the highest dose tested (1.2×10^{11} vp). In a combined embryo-fetal and pre- and postnatal development GLP study in female rabbits with another Ad26-based vaccine (Ad26.ZEBOV, encoding an Ebola virus antigen), there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period. A repeated dose and local tolerance GLP study, and a combined embryo-fetal and pre- and postnatal development GLP study with Ad26.COV2.S are planned to run in parallel with study VAC31518COV1001.

Clinical Studies

At the time of initial protocol writing, no clinical data with the Ad26.COV2.S vaccine were available.

Several clinical studies with Ad26.COV2.S will be ongoing at the time of initiation of study VAC31518COV3009.

The FIH study VAC31518COV1001 is a randomized, double-blind, placebo-controlled, Phase 1/2a multicenter study in adults aged ≥18 to ≤55 years and aged ≥65 years. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S will be evaluated at 2 dose levels (5×10^{10} vp and 1×10^{11} vp), administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in 1 cohort.

The safety, reactogenicity, and immunogenicity will be evaluated in a cohort of adults aged ≥18 to ≤55 years (Cohort 1a). Safety, reactogenicity, and immunogenicity will also be evaluated in an expanded cohort in this age group (Cohort 2). In addition, safety, reactogenicity, and immunogenicity will be evaluated in a cohort of adults aged ≥65 years (Cohort 3). Overall, a target of 1,045 adult participants in these 2 age groups will be randomly assigned in this study.

As of 10 September 2020, a single injection of Ad26.COV2.S has been administered to 805 adult participants, aged 18 and older in the FIH study VAC31518COV1001.

At the time of protocol Amendment 1 writing, initial immunogenicity and safety data (28 days post-Dose 1 data from Cohort 1a [participants aged ≥18 to ≤55 years] and available data from Cohort 3 [participants aged ≥65 years]) from study VAC31518COV1001 have become available and demonstrate that a single dose of Ad26.COV2.S at 5×10^{10} virus particles (vp) and 1×10^{11} vp induces an immune response that meets prespecified minimum criteria and has an acceptable safety profile. These data support the sponsor's decision to proceed with Ad26.COV2.S at a dose level of 5×10^{10} vp in its Phase 3 studies.

Refer to the latest IB and its addenda (if applicable) for a high level description of the additional ongoing studies with Ad26.COV2.S.[34]

Clinical Safety Experience With Ad26-based Vaccines

As described above, replication-incompetent Ad26 is being used as a vector in the development of vaccine candidates against diseases such as malaria, RSV, HIV, Ebola virus, Zika virus, and filovirus.

As of 01 July 2020, Ad26-based vaccines had been administered to approximately 90,000 participants in ongoing and completed studies, including more than 76,000 participants in an ongoing Ebola vaccine study in the Democratic Republic of the Congo (VAC52150EBL3008/DRC-EB-001) and an ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign).

The sponsor's clinical AdVac® safety database report (V5.0, dated 10 April 2020, cut-off date 20 December 2019) describes integrated safety data from 26 completed clinical studies using Ad26-based vaccines for which the database was locked for final analysis. In these 26 studies, 4,224 adult participants were vaccinated with an Ad26-based vaccine and 938 adult participants received a placebo. A total of 6,004 Ad26-based vaccine doses were administered to adults. Most adult participants (3,557 out of 4,224; 84.2%) received Ad26-based vaccine at a dose level of 5×10^{10} vp, while 284 adult participants (6.7%) received Ad26-based vaccine at the 1×10^{11} vp dose level (the highest dose level tested).

As of 01 July 2020, more than 85,000 participants were enrolled in ongoing studies and the ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign). However, their safety data were not included in the AdVac® safety database report V5.0 because the studies were still blinded, the studies were unblinded but their analysis took place after the AdVac® safety database report cut-off date, or the study data were not integrated in the Ad26-based vaccine database used for the report.

Overall, the Ad26-based vaccines were well tolerated irrespective of the antigen transgene, without significant safety issues identified to date. See Section 2.3.1 for a summary of data from the AdVac® safety database report.

Ad26-based Vaccines in Adults Aged 60 Years and Older

In the RSV vaccine clinical development program, Ad26.RSV.preF has been evaluated in studies in participants aged ≥60 years, including the Phase 1 studies VAC18193RSV1003 and VAC18193RSV1005, Phase 1/2a study VAC18193RSV1004, Phase 2a study VAC18193RSV2003, and Phase 2b study VAC18193RSV2001. Up to a cut-off date of 24 April 2020, approximately 3,700 participants aged ≥60 years have received an Ad26.RSV.preF-based regimen in completed and ongoing studies. An acceptable safety and reactogenicity profile in participants aged ≥60 years has been reported for the Ad26.RSV.preF-based regimens assessed in these studies, and no safety concerns have been raised to date.

Th1/Th2 Profile of Ad26-based Vaccines in Clinical Studies

In the 1960s, a formalin-inactivated RSV vaccine was associated with enhanced respiratory disease (ERD) in young children, characterized by an increased rate of RSV-mediated, severe lower respiratory tract infection in the vaccinated individuals compared with the control group.[18,28,37,38] Although the mechanisms for ERD are not fully understood, it is thought that FI-RSV may have: 1) failed to induce adequate neutralizing antibody titers; 2) led to an overproduction of binding antibodies promoting immune complex deposition and hypersensitivity reactions; 3) failed to induce adequate numbers of memory CD8+ T cells important for viral clearance; and 4) induced a Th2-skewed type T-cell response.[47] Vaccine-induced ERD has also been described for SARS-CoV and MERS-CoV in animal models,[34] but proof of human SARS-CoV or MERS-CoV vaccine-associated enhanced disease does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. For SARS and MERS, the mechanism of enhanced disease observed in mice has been associated with a Th2-mediated eosinophilic infiltration in the lung, which is similar to the ERD effects observed after RSV infection of mice immunized with FI RSV.

Similar to RSV vaccines, enhanced disease has been shown for whole-inactivated SARS-CoV vaccines, as well as subunit vaccines inducing a Th2-type immune response, which can be rescued by formulating vaccines in Th1-skewing adjuvants. In addition to a Th1-biased immune response, also induction of a high proportion of neutralizing antibodies compared with virus binding antibodies is desirable to prevent predisposition to enhanced disease as observed for RSV vaccines. While vaccine-associated enhanced disease was observed in nonclinical studies with experimental SARS and MERS vaccines, it is not a given that the same risk applies to COVID-19 vaccines. To the sponsor's knowledge, antibody-related COVID-19 disease enhancement has not been observed in nonclinical models yet. Antibodies against the receptor-binding domain of SARS-CoV-2 were shown not to enhance in vitro infectivity. Repeated SARS-CoV-2 challenge of NHP or NHP studies with Th2 biasing COVID-19 vaccines that would be expected to predispose to enhanced disease did not show any signs of enhanced disease. In addition, disease enhancement was not observed in NHP immunized with ChAdOx1 encoding SARS-CoV-2 S protein prior to challenge with SARS-CoV-2.[34]

The immunogenicity profile of adenoviral vectors, with particular emphasis on Th1 responses, is illustrated by data obtained from immunization of adults with Ad26-vectored HIV vaccines (Ad26.ENVA.01 and Ad26.Mos.HIV) and Ad26-vectored Ebola vaccine (Ad26.ZEBOV). These data show predominantly IFN-γ and TNF-α production in $CD4^+$ and $CD8^+$ T cells.[2,3,4] In the RSV vaccine clinical development program, Ad26.RSV.preF is being evaluated in healthy RSV-seropositive toddlers aged 12 to 24 months (Phase 1/2a study VAC18194RSV2001). Safety data from the PA at 28 days after the second study vaccination revealed no safety concerns following Ad26.RSV.preF dosing at 5×10^{10} vp or a placebo. The immunogenicity of a single immunization with Ad26.RSV.preF in RSV-seropositive toddlers aged 12 to 24 months, including favorable Th1 bias, was confirmed. In a further study of Ad26.RSV.preF in RSV-seronegative toddlers aged 12 to 24 months (Phase 1/2a study VAC18194RSV2002), initial safety data have not revealed concerns after Ad26.RSV.preF dosing.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of Ad26.COV2.S may be found in the IB.[34]

2.3.1 Risks Related to Study Participation

The following potential risks of Ad26.COV2.S will be monitored during the study and are specified in the protocol.

Risks Related to Ad26.COV2.S

No clinical data with Ad26.COV2.S are available at the time of finalization of the initial VAC31518COV3009 protocol.

For emerging clinical data and the most comprehensive nonclinical information regarding Ad26.COV2.S, refer to the latest version of the IB and its addenda (if applicable).[34]

Sites should advise participants that side effects include fever as well as fatigue, myalgia, and headache per the current ICF; however, the occurrence of fever appears to be more common in younger adults and can be severe. This is based on information from study VAC31518COV1001 that became available at the time of protocol Amendment 1 writing.

Risks Related to Adenoviral-vectored Vaccines

The clinical AdVac® safety database (report version 5.0, dated 10 April 2020, cut-off date 20 December 2019) contains pooled safety data from 26 Janssen-sponsored clinical studies with Ad26 vaccine candidates: Ad26.ZEBOV (Ebola; 10 studies), Ad26.ENVA.01, Ad26.Mos.HIV and Ad26.Mos4.HIV (HIV; 8 studies), Ad26.CS.01 (malaria; 1 study), Ad26.RSV.FA2 and Ad26.RSV.preF (RSV; 6 studies), and Ad26.Filo (filovirus; 1 study). In these studies, 4,224 adult participants and 650 children received at least 1 vaccination with an Ad26-based vaccine. The AdVac® safety database report includes data only from studies for which the database has been locked for the final analysis; therefore, of the studies including an Ad26.RSV.preF-based regimen mentioned in Section 2.2, only data for approximately 230 participants aged ≥60 years from studies VAC18193RSV1003, VAC18193RSV1005, and VAC18193RSV2003 were included.

Overall, the Ad26-based vaccines were well tolerated, without significant safety issues identified.

The majority of solicited local and systemic AEs were of mild or moderate severity and usually started within 1 to 2 days after vaccination. Most of the events resolved within 1 to 3 days.

In adults, the most frequently reported solicited local AE was injection site pain (56.9% of Ad26 participants, compared with 22.5% of placebo participants). All other solicited local AEs were experienced by less than 25% of adult participants. The most frequently experienced solicited local AE in children was injection site pain, reported in 13.9% of children aged 1-3 years, 29.8% of children aged 4 to 11 years, and 24.8% of children aged 12 to 17 years after vaccination with an Ad26-based vaccine. For placebo, these percentages were 29.2% in children aged 4 to 11 years and 14.3% in children aged 12 to 17 years. No children aged 1 to 3 years have received placebo.

Severe injection site pain was experienced by 1.0% of adult Ad26 participants and 0.8% of children aged 4 to 11 years. No children in the other 2 age groups and no placebo participants experienced severe injection site pain.

There was a trend toward an increase in the frequency of some local AEs with an increase in Ad26 dose, ie, injection site pain (18.7% of participants at the 0.8×10^{10} vp dose level, 38.7% of participants at the 2×10^{10} vp dose level, 52.0% of participants at the 5×10^{10} vp dose level, and 77.1% of participants at the 1×10^{11} vp dose level), and to a lesser extent injection site swelling (6.7%, 2.7%, 9.3%, and 17.6%, respectively). Injection site warmth was not collected at the 0.8×10^{10} vp and the 2×10^{10} vp dose level. The frequency of injection site warmth at the 5×10^{10} vp and the 1×10^{11} vp dose level was 19.5%, and 26.7%, respectively. This trend needs to be interpreted with caution since the participants in the lower dose groups (0.8×10^{10} vp and 2×10^{10} vp dose level) were all from a single study (VAC52150EBL3002), and the majority of the participants in the highest dose group (1×10^{11} vp dose level) were also from a single study (VAC18193RSV2003).

The most frequently reported solicited systemic AEs (ie, reported in more than 30% of participants) for adult Ad26 participants were malaise (53.8%), fatigue (48.3%), headache (45.7%), and myalgia (38.3%), all of which were more frequent for Ad26 participants compared with placebo (36.4%, 30.7%, 30.0%, and 17.7% of placebo participants, respectively). Most of these events were considered related to the study vaccine. Pyrexia (9.9%) and vaccine-related pyrexia (9.0%) were also reported more frequently after administration of an Ad26-based vaccine compared with placebo (3.5% and 2.9%, respectively).

Solicited systemic AEs reported in ≥10% of children aged 1 to 3 years were decreased appetite (13.9%), decreased activity (13.2%), pyrexia (11.1%), and irritability (10.4%). The most frequently reported solicited systemic AEs in children aged 4 to 11 years (reported in ≥15% of Ad26 participants) were headache (23.6%; no data are available for the placebo group in this age group), and decreased activity (18.5%) and irritability (17.6%), which were both reported in 4.2% (N=1) of placebo participants. The most frequently reported solicited systemic AEs in children aged 12 to 17 years (reported in ≥15% of Ad26 participants) were headache (34.6%) and fatigue (24.0%), compared to 33.3% and 19.0% of placebo participants, respectively. Most of the frequently experienced solicited systemic AEs in children were considered related to the study vaccine.

The majority of solicited systemic AEs were of mild or moderate severity. For adults, 6.5% of Ad26 participants and 2.0% of placebo participants reported severe solicited systemic AEs, mostly malaise and fatigue. Other severe solicited systemic AEs were reported in less than 3% of adult Ad26 participants.

There was a trend toward an increase in the frequency of solicited systemic AEs with an increase in Ad26 dose (35.3% at the 0.8×10^{10} vp dose level, 49.3% at the 2×10^{10} vp dose level, 64.5% at the 5×10^{10} vp dose level, and 70.4% at the 1×10^{11} vp dose level). The frequency of severe solicited systemic AEs also tended to increase with higher Ad26 dose, ie, 1.3% of participants at the 0.8×10^{10} vp and the 2×10^{10} vp dose level, 5.3% of participants at the 5×10^{10} vp dose level, and 14.4% of participants at the 1×10^{11} vp dose level. This trend needs to be interpreted with caution since the participants in the lower dose groups (0.8×10^{10} vp and 2×10^{10} vp dose level) were all from a single study (VAC52150EBL3002), and the majority of the participants in the highest dose group (1×10^{11} vp dose level) were also from a single study (VAC18193RSV2003).

The most frequently reported unsolicited AE in adult Ad26 participants was upper respiratory tract infection (5.3% vs. 7.0% in adult placebo participants). The most frequently reported unsolicited AEs considered related to the vaccine were neutropenia (1.0% of adult Ad26 participants vs. 0.5% of adult placebo participants) and dizziness (0.7% vs. 0.2%, respectively).

For Ad26, the most frequently reported unsolicited AE in children was malaria,[a] reported in 36.8% of children aged 1 to 3 years, in 19.0% of children aged 4 to 11 years, and in 10.6% of children aged 12 to 17 years. One child in the 12 to 17 years group (4.8%) experienced malaria after placebo vaccination. There were no other children in the placebo groups who experienced malaria. The most frequently reported related unsolicited AE was hypernatremia (1.6% of children aged 4 to 11 years [vs. 4.2% with placebo] and 2.4% of children aged 12 to 17 years [vs. 4.8% with placebo]). No AEs in children aged 1 to 3 years were considered related to the vaccine.

General Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine and/or placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored, but are generally short-term. Instructions regarding use of antipyretic medication can be found in Section 6.8.

Syncope can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria, or even anaphylaxis. Severe reactions are rare. Participants with 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), will be excluded from the study.

After each vaccination, participants will remain at the study site for close observation by study staff to monitor for the development of any acute reactions. The first 1,000 participants will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 1,000 participants no acute reactions have been observed, the observation period at the study site may be reduced to at least 15 minutes after each vaccination for the remaining participants in the study. Necessary emergency equipment and medications must be available in the study site to treat severe allergic reactions.

[a]This was expected as the pediatric studies were conducted in malaria-endemic regions. The imbalance in the frequency of malaria between Ad26 participants and placebo participants can largely be explained by the fact that the active control group of study VAC52150EBL3001 was not included in the pooling.

Pregnancy and Birth Control

The effect of the study vaccine on a fetus or on nursing baby is unknown.

Given the limited number of incident pregnancies in the clinical studies with Ad26-based vaccines in the AdVac® safety database report (HIV vaccine: 20 pregnancies in participants and 10 in partners of participants; Ebola vaccine: 32 pregnancies in participants and 13 in partners of participants), it is not possible at present to draw firm conclusions on the safety of the vaccines when administered around the time of conception or prior to the initiation of the pregnancies. There is currently no concerning pattern of AEs in the pregnancies initiated around the time of vaccination or after exposure to the Ad26-based vaccines in the Janssen vaccines clinical development programs.

Participants of childbearing potential will be required to agree to practicing an acceptable effective method of contraception and agree to remain on such a method of contraception from providing consent until 3 months after receiving the last dose of the study vaccine (see Section 5.1). Use of condoms is not considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms.[74] Participants who are pregnant will be excluded from the study. Participants who become pregnant during the study will not receive further vaccination but will remain in the study and will continue to undergo all procedures for surveillance and follow-up of COVID-19 and all safety follow-up as outlined in the protocol for all participants.

Participants who are breastfeeding are allowed to participate in the study.

Risks from Blood Draws

Blood draws may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and rarely, infection at the site where the blood is taken.

Risks from Collection of Nasal Swab Samples

Collection of a nasal swab sample may cause a nosebleed.

Participants are asked to perform the nasal swab samples themselves at home or to seek assistance from a trained health care professional (HCP). Assistance with the collection of nasal swab samples bears the risk of potentially infecting the assistant.

Theoretical Risk of Enhanced Disease

Vaccine-associated enhanced disease has been described for SARS-CoV and MERS-CoV in some animal models[1,7,22,31,32], and is associated with non-neutralizing antibodies and a Th2-skewed immune response. In contrast, the Ad26-based vaccines have been shown to induce a clear Th1-skewed immune response and generate potent neutralizing antibody responses in both humans and animal models (see Section 2.2). Participants in the present study will be informed of the theoretical risk of disease enhancement in the informed consent form (ICF). Initially, this study will include healthy adults aged ≥18 to <60 years of age and healthy elderly ≥60 years of age (Stage 1). As a risk mitigation strategy, all enrolled participants will be intensively monitored during the conduct of the study to rapidly diagnose COVID-19 and refer for treatment, if

applicable. In case of any new symptoms or health concerns that could be related to infection with SARS-CoV-2, participants will be evaluated for acquisition of molecularly confirmed COVID-19 and severity will be assessed using the case definitions specified in Section 8.1.3 by the investigator as well as by the clinical evaluation committee (CEC) (see Section 8.1.3.6), as part of the primary and secondary endpoints (see Section 3). All participants will be monitored for safety (including enhanced disease) for 2 years after the last vaccination, ie, until the last study visit. In addition, as detailed in Section 9.8, the statistical support group (SSG) will monitor the number and severity of molecularly confirmed COVID-19 cases in the Ad26.COV2.S and placebo groups to identify an imbalance between groups if it occurs. The SSG will inform the IDMC as soon as an imbalance between groups is detected. A prespecified threshold (imbalance above a certain percentage and/or number of cases) that will trigger notification of the IDMC will be described in the SAP.

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the investigators and participants will be informed.

2.3.2 Benefits of Study Participation

Participants may benefit from clinical testing and physical examination.

The clinical benefits of Ad26.COV2.S have yet to be established. Currently, there are no effective vaccines for the prevention of COVID-19 and no efficacy can be concluded from current data. The overall benefit and risk balance for individual participants thus cannot be ascertained. Participants must be informed that this vaccine has not yet been proven to be effective, and it should be assumed that it is not the case until clinical studies are conducted to demonstrate its effectiveness.

2.3.3 Benefit-Risk Assessment of Study Participation

Based on the available data and proposed safety measures, the overall benefit-risk assessment for this clinical study is considered acceptable for the following reasons:

- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:
  - In general, safety evaluations will be performed at scheduled visits during the study, as indicated in the Schedules of Activities.
  - The first 1,000 participants will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 1,000 participants no acute reactions have been observed, the observation period at the study site may be reduced to at least 15 minutes after each vaccination for the remaining participants in the study. Necessary emergency equipment and medications must be available in the study site to treat severe

allergic reactions. Participants in the Safety Subset will use an e-Diary to document solicited signs and symptoms. Details are provided in Section 8.3.

- The investigator or the designee will document unsolicited AEs for participants in the Safety Subset, and SAEs and medically-attended adverse events (MAAEs) for all participants as indicated in Section 8.3 and Appendix 4.
- Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until clinically stable.
- An IDMC will be established to monitor safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. This committee will review interim unblinded data. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter. Additional ad hoc review may be performed further to the occurrence of any SAE leading to a study pausing situation as outlined in Section 6.9, or at request of the sponsor's medical monitor or designee.

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - The study will use a staggered enrollment strategy to mitigate the risks for participants at increased risk of progression to severe COVID-19:
    - In Stage 1, the study will initially enroll participants based on acceptable Day 29 post-Dose 1 immunogenicity and safety data from Cohorts 1a and 3 of study VAC31518COV1001 (see details in the IB[33,34]). In this stage, approximately 1,000 participants without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including approximately 500 Ad26.COV2.S recipients and approximately 500 placebo recipients;).
    - In Stage 2, after a vaccination pause in Stage 1 to allow the IDMC to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing studies) and if no safety concerns are identified, enrollment will proceed, also including participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19 in 2 age-dependent subgroups (≥18 years to <60 years of age and ≥60 years of age). See Section 1.2 (Figure 1) for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities.
  - Participants will be intensively monitored in this study to rapidly diagnose COVID-19, and refer for treatment, if applicable. This will mitigate the theoretical potential risk for vaccine-associated enhanced disease when immunized individuals are infected with the virus. The induction of neutralizing antibody and the Th1 response induced by this vaccine in animals also mitigates this risk.
  - There are prespecified rules for participants in Stage 1 that if met would result in pausing of further vaccinations (see Section 6.9), preventing exposure of new participants to study vaccine until the IDMC reviews all safety data (see Committees Structure in Appendix 3 [Section 10.3.6]).
  - Study vaccinations will be discontinued in participants for the reasons included in Section 7.
  - Contraindications to vaccination are included in Section 5.5.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b], as compared to placebo, in SARS-CoV-2 seronegative adults	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days after the 2nd vaccination (Day 71).
Secondary[f] *(The method used to perform hypothesis testing preserving the family-wise error rate [FWER] will be specified in the Statistical Analysis Plan [SAP])*	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b], as compared to placebo, in adults regardless of their serostatus	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 1 day after the 1st vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 14 days after the 2nd vaccination (Day 71)
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b] as compared to placebo	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after the 1st vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 14 days after the 1st vaccination (Day 15)
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, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) and linked to any molecularly confirmed[a], COVID-19[b,c] at least 14 days after the 2nd vaccination (Day 71)
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral RNA load compared to placebo for moderate to severe/critical COVID-19[b]	Assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed[a], moderate to severe/critical COVID-19[b] by serial viral load measurements during the course of a COVID-19 episode, at least 14 days after the 2nd vaccination (Day 71)
To assess the effect of Ad26.COV2.S on molecularly confirmed[a], mild COVID-19[c]	First occurrence of molecularly confirmed[a], mild COVID-19[c], at least 14 days after the 2nd vaccination (Day 71)
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the US FDA harmonized case definition[d]	First occurrence of molecularly confirmed[a] COVID-19[d] at least 14 days after the 2nd vaccination (Day 71)

Objectives	Endpoints
To assess the effect of Ad26.COV2.S on all molecularly confirmed[a] symptomatic COVID-19[b,c], as compared to placebo	Burden of disease (BOD) endpoint (see Section 9.5.2) derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 14 days after the 2nd vaccination (Day 71)
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo[e]	Serologic conversion between baseline (Day 1; before 1st vaccination) and 14 days, 6 months and 1 year after the 2nd vaccination using an 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[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 14 days after the 2nd vaccination (Day 71)
Safety	
To evaluate safety in terms of SAEs (during the entire study), MAAEs (until 6 months after the last vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months after the last vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic AEs during 7 days after each vaccination, and in terms of unsolicited AEs during 28 days after each vaccination	Occurrence, intensity, duration and relationship of solicited local and systemic AEs during 7 days following each vaccination and of unsolicited AEs during 28 days following each 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	
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral RNA load compared to placebo for mild COVID-19[c]	Assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed[a], mild COVID-19[c] by serial viral load measurements during the course of a COVID-19 episode
To assess the effect of Ad26.COV2.S on health care utilization (such as hospitalization, ICU admission, ventilator use) linked to any molecularly confirmed[a] COVID-19, as compared to placebo	Health care utilization (such as hospitalization, ICU admission, ventilator use) linked to any molecularly confirmed[a] COVID-19 at least 14 days after the 2nd vaccination (Day 71)
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection in participants with comorbidities associated with increased risk of	First occurrence of SARS-COV-2 infection (serologically and/or molecularly confirmed[a]) in participants with comorbidities associated with increased risk of progression to severe COVID-19

Objectives	Endpoints
progression to severe COVID-19, as compared to placebo	with onset at least 14 days after the 2nd vaccination (Day 71)
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[a] 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 confirmed[a] COVID-19, with onset at least 14 days after the 2nd vaccination (Day 71)
To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo	Deaths occurring at least 14 days after the 2nd vaccination (Day 71)
To evaluate the immune response in participants with COVID-19 in relation to risk of development of COVID-19, protection induced by Ad26.COV2.S, and risk of accelerated disease	Assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, , with the risk of COVID-19 and protection induced by the study vaccine
In a subset of participants to further assess the humoral immune response to Ad26.COV2.S, as compared to placebo	Humoral immunogenicity endpoints: • Functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire • SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein) • Adenovirus neutralization as measured by VNA • Analysis of antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein
To explore changes in the SARS-CoV-2 genome	Development of SARS-CoV-2 variants
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 to 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 Ad26.COV2.S as compared to placebo	Reduction in severity of COVID-19 signs and Symptoms
To evaluate the occurrence, severity, and duration of COVID-19 episodes in participants who received Ad26.COV2.S, as compared to placebo, as assessed by a clinical evaluation committee (CEC)	Occurrence, severity, and duration of COVID-19 episodes, as assessed by a CEC

Objectives	Endpoints
To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity	Analysis of antibodies binding to coronaviruses other than SARS-CoV-2 by ELISA
To assess the incidence of co-infection of SARS-CoV-2 and other respiratory pathogens and to assess the effect of the vaccine during such co-infections as well as to estimate the incidence of other respiratory pathogens during the study period.	Analysis of broad respiratory pathogens panel in the nasal swabs collected during a confirmed COVID-19 episode and in a subset of nasal swab samples from participants with a symptomatic infection.
In US participants, To increase the information on prior medical history (electronic health records, claims, laboratory data from other care settings) in order to further evaluate its potential effect on the response to immunization and the impact of immunization on efficacy and duration of efficacy as well as AEs that may occur during and after completion of the study.	Utilization of tokenization and matching procedures for exploratory analysis of participant's medical data prior to, during, and following participation in the study (real-world data). Analysis will be performed to relate real-world data to vaccine immune responses, efficacy and duration of protection, and AEs (see Section 4.1 and Section 8.7).

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result by a central laboratory using a PCR-based or other molecular diagnostic test.
[b] Per case definition for moderate to severe/critical COVID-19 (see Section 8.1.3.1).
[c] Per case definition for mild COVID-19 (see Section 8.1.3.2).
[d] Per case definition for COVID-19 according to the US FDA harmonized case definition (see Section 8.1.3.3)
[e] Per case definition for asymptomatic or undetected COVID-19 (see Section 8.1.3.4)
[f] All secondary efficacy endpoint analyses will occur in the PP analysis set, in seronegative participants unless otherwise indicated in the statistical analysis plan (SAP).

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESES

The study is designed to test the primary hypothesis of vaccine efficacy (VE) in the per-protocol (PP): H0: VE ≤30% versus H1: VE >30% and will be evaluated at a 2.5% one-sided significance level.

The primary endpoint will evaluate the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition (Section 8.1.3.1), with onset at least 14 days after the 2nd vaccination with Ad26.COV2.S versus placebo, in the PP population including all events with and without comorbidities.

If the primary endpoint hypothesis testing is successful, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%. The method to perform hypothesis testing of primary and secondary objectives preserving the FWER will be specified in the SAP. The FWER will be controlled at 2.5%.

Details are described in the Section 9.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S will be evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine.

Initial immunogenicity and safety data (28 days post-Dose 1 data from Cohort 1a and available data from Cohort 3) from study VAC31518COV1001 have demonstrated that a single dose of Ad26.COV2.S at 5×10^{10} vp and 1×10^{11} vp induces an immune response that meets prespecified minimum criteria and has an acceptable safety profile. The sponsor has therefore decided to proceed with the Ad26.COV2.S at a dose level of 5×10^{10} vp in its Phase 3 studies. Even though a single-dose regimen in study VAC31518COV1001 showed good immunogenicity that may already protect against COVID-19, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in an increased and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study. The single dose regimen will be further evaluated in study VAC31518COV3001.

The study will consist of a screening phase of up to 28 days, a 60-week double-blind study period (including the administration of 2 doses of study vaccine [1 dose on Day 1 and 1 dose on Day 57], after randomization), and a long-term follow-up period of 1 additional year. The duration of individual participation, including screening, will be maximum 2 years and 3 months. If a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted. The end-of-study is considered as the completion of the last visit for the last participant in the study.

Participants will be randomized in parallel in a 1:1 ratio to receive Ad26.COV2.S or placebo intramuscularly (IM) as shown in Table 1. Ad26.COV2.S will be administered at a dose level of 5×10^{10} vp.

Table 1: Vaccination Schedule VAC31518COV3009

Group	N	Day 1	Day 57
1	15,000	Ad26.COV2.S (5×10^{10} vp)	Ad26.COV2.S (5×10^{10} vp)
2	15,000	Placebo	Placebo

N = number of participants; vp = virus particles.

Note: It is intended that a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be ≥18 to <40 years of age.

A staggered enrollment strategy will be used:

- Stage 1: Initially, approximately 1,000 participants without comorbidities that are associated with increased risk of progression to severe COVID-19 (including approximately 500 Ad26.COV2.S recipients and approximately 500 placebo recipients) will be enrolled).
- Stage 2: After a vaccination pause in Stage 1, to allow the IDMC to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing studies) and if no safety concerns are identified enrollment will proceed, expanding enrollment to include participants with and without comorbidities that are associated with increased risk of progression to severe

COVID-19 in 2 age-dependent subgroups (≥18 years to <60 years of age and ≥60 years of age). See Section 1.2 (Figure 1) for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities.

Overall, a target of 30,000 adult participants (≥18 to <60 years of age and ≥60 years of age, with and without relevant comorbidities) will be randomly assigned in this study, under the assumption that the annualized incidence of moderate to severe/critical COVID-19 (meeting the COVID-19 case definition for the primary endpoint) will be approximately 1% to 4% at the start of the study. Every effort will be made to identify regions of high SARS-CoV-2 activity and populations within these regions with high risk of exposure to the virus will be enrolled. Recruitment for high incidence populations will also take into account age. Per stage, participants will be enrolled in 2 subgroups (≥18 to <60 years of age and ≥60 years of age).

This sample size takes into consideration the uncertainty of the epidemiological situation in combination with the ability to provide a high probability (approximately 90%) to reach a time to signal within 15 months of the last study for a vaccine with an assumed 65% VE or higher. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender.

Of the total sample size, a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be <40 years of age. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender. Refer to Section 9.2.1 for details about the sample size determination.

All participants will be actively and passively followed for acute molecularly confirmed, symptomatic COVID-19, regardless of severity. Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result by a central laboratory using a PCR-based or other molecular diagnostic test.

The primary objective will be evaluated in real-time manner through sequential testing of accumulating primary endpoints through the SSG and IDMC. As soon as a decision is reached, the Sponsor Committee will be alerted who can initiate internal decision procedures to trigger health authority interactions based on the outcome of the study. The study team will remain blinded until the database for primary analysis is locked. Further details are described in Section 9.5.1.

Key efficacy assessments include the (suspected) COVID-19 surveillance (symptom check), recording of COVID-19-related hospitalizations and complications, and the laboratory confirmation of SARS-CoV-2 infection by a molecular assay (based on RT-PCR) and by anti-SARS-CoV-2 serology (see Section 8.1.2). Immunogenicity assessments, and especially assessments of the humoral immune responses with emphasis on neutralizing and binding antibodies will also be performed (see Section 8.1.4). Key safety assessments will include the monitoring of solicited and unsolicited AEs (in the Safety Subset only), and the collection of SAEs and MAAEs in all participants (see Section 8.3). The viral load of SARS-CoV-2 will be assessed in confirmed COVID-19 cases (see Section 8.4). Medical resource utilization (MRU) following vaccination will be recorded for all participants with molecularly confirmed, symptomatic COVID-19 (see Section 8.5). Additional characteristics related to current work situation, living situation, and community interactions will be collected for risk factor analyses, if allowed per local

regulations. Participants who consent to this will be interviewed on these aspects prior to vaccination on Day 1 and, at other timepoints, on changes compared to Day 1 (See Appendix 12). In the US, for consenting participants, medical data (electronic health records, claims, laboratory data from other settings) from 5 years prior to study enrollment until 5 years after study completion may be accessed utilizing tokenization and matching procedures (see sections 4.2 and 8.7). These data together with prior medical history data collected at study entry may be used for exploratory analyses to enhance our understanding of the potential impact of prior medical history on the response to immunization and the impact of immunization on efficacy and duration of efficacy as well as adverse events that may occur during and after completion of the study.

The first 1,000 participants will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 1,000 participants no acute reactions have been observed, the observation period at the study site may be reduced to at least 15 minutes after each vaccination for the remaining participants in the study. After each vaccination, for participants in the Safety Subset, solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, and concomitant therapies will be documented by study-site personnel following this observation period. Participants in the Safety Subset will also record solicited signs and symptoms in an e-Diary for 7 days post-vaccination. The reporting periods of unsolicited AEs, MAAEs, SAEs, and special reporting situations are detailed in Section 8.3. Reporting periods for concomitant therapy are outlined in Section 6.8.

All participants will be followed-up until 2 years after the 2nd study vaccination to monitor for signs and symptoms of COVID-19 (to determine duration of protection) and to monitor for safety (including enhanced disease). The approach for the analysis of this long-term follow-up cohort for safety and VE will be provided in detail in the analytic plan. Participants in the Immunogenicity Subset will be followed-up for long-term immunogenicity. Participants will also be monitored for complications potentially associated with COVID-19 (such as but not limited to hyperinflammatory syndrome, pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death)[62], and for MRU (such as rates of ICU admission, ventilator use).

Until 1 year after the 2nd vaccination, each participant will be asked at least twice a week, through the electronic clinical outcome assessment (eCOA), if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. As of 1 year after the 2nd vaccination, until the end of the 2-year follow-up period, the frequency of this (suspected) COVID-19 surveillance (symptom check) through the eCOA will decrease to once every 2 weeks. Every effort will be made to document the status of all participants that are lost to follow-up due to not completing the eCOA and for whom hospitalization has not been recorded.

Enrolled participants will be counselled on SARS-COV-2 infection prevention each time that they have a contact with site staff, in line with local guidelines.

At the time of study entry, each participant will need to indicate to the study site, in case they would get infected with SARS-CoV-2, the identity and location of their routine medical care physician and/or facility and the identity and location of where they would obtain emergency care and hospitalization if necessary. If this information is not available, a plan for where such care could be obtained should be developed. If a participant should have COVID-19 and their symptoms deteriorate, they will be instructed to go to the HCP or hospital that has been identified in advance.

All participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19[a] (see Section 8.1.1) and all participants with at least one positive RT-PCR test for SARS-CoV-2 on COVID-19 Day 1-2 and Day 3-5 visits should undertake the COVID-19 procedures (see Section 8.1.2 and Section 1.3) until 14 days after symptom onset (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last. However, participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19[a] should stop the COVID-19 procedures as soon as it is confirmed that both nasal swabs collected on COVID-19 Day 1-2 and Day 3-5 are negative for SARS-CoV-2. Resolution of the COVID-19 episode is defined as having 2 consecutive SARS-CoV-2 negative nasal swabs and 2 consecutive days with no COVID-19-related signs or symptoms. At the time of resolution of the COVID-19 episode, the collected information will be applied against the clinical case definition (Sections 8.1.3.1, 8.1.3.2, and 8.1.3.3).

Site staff and participants will not be blinded as to the outcome of the molecular test results from the local (hospital) laboratory and the baseline molecular test results from a central laboratory. Their routine health care professional (HCP) can obtain external diagnostics, including RT-PCR or other molecularly confirmed viral tests, as medically needed.

The occurrence of molecularly confirmed COVID-19, all complications associated with COVID-19, and concomitant therapies associated with COVID-19 will be captured in the electronic case report form (eCRF) for the duration of the study. Every effort will be made to capture medical information from any medical visits (eg, visits to the primary care providers, emergency department/urgent care clinic visits, etc.) related to COVID-19 or its complications via the medically-attended COVID-19 form (MA-COV form) (see Appendix 8).

All necessary precautions (as per local regulation) should be taken to protect medical staff and other contacts of participants who are suspected to have COVID-19 until proven negative by molecular techniques or who are positive until they are no longer positive. In the event of a confirmed SARS-CoV-2 infection, the participant and the participant's medical care provider and/or local health authorities (if required) will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

[a] As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19.

Additional study procedures and assessments for immunogenicity and safety (reactogenicity and unsolicited AE) will be performed in subsets of participants (see Section 8.1.4 and Section 8.3).

An IDMC will be commissioned for this study. Refer to Section 9.8 and Appendix 3 for more details.

A diagram of the study design is provided in Section 1.2.

4.2. Scientific Rationale for Study Design

Vector Selection

The rationale behind the selection of the Ad26 vector is described in Section 2.

Dose Selection

The rationale behind the selection of the dose is described in Section 4.3.

Blinding, Control, Study Phase/Periods, Vaccine Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical and immunological endpoints that may occur in the absence of active vaccine.

Randomization will be used to minimize bias in the assignment of participants to vaccine groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across vaccine groups, and to enhance the validity of statistical comparisons across vaccine groups. Blinded study vaccine will be used to reduce potential bias during data collection and evaluation of study endpoints.

Blinding will be guaranteed by the preparation of the study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation and dispensing, and by the administration of vaccine in a masked syringe by a blinded study vaccine administrator. Participants will be randomly assigned to 1 of the groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor and using the interactive web response system (IWRS) (see also Section 6.3).

Medical Resource Utilization Data Collection

Prophylaxis of COVID-19 with Ad26.COV2.S may reduce the need for and duration of supportive care (eg, hospitalization, oxygen supplementation). The study will evaluate the impact of Ad26.COV2.S versus placebo on the development and clinical course of COVID-19.

Participant Medical Information Prior to, During and After the Study (Real-world Data) (For US Participants Only)

Real-world data plays a critical role in improving understanding of factors that may influence response to immunization and the effectiveness and safety of a vaccine product during and after completion of the study. This may be important in gaining insight in terms of duration of efficacy and incidence of adverse events after study completion. This may be especially important in the

event that efficacy of Ad26.COV2.S or another vaccine is shown and follow-up in a randomized manner is compromised.

To allow the linking of participant records from different sources, ie, data collected as part of the study as specified in the Schedules of Activities and longitudinal real-world data (from 5 years prior to enrollment in the study until 5 years after study completion) such as electronic health record, claims, and laboratory data from other care settings, without compromising the participant's confidentiality, tokenization and matching procedures will be utilized **for US participants only**. The tokenization process starts with each data provider generating a token behind the firewall via a proprietary software. Personal information such as names and dates of birth from study participants are removed from real-world data sources and replaced with encrypted, one-way, hashed identifiers, and then further encrypted using asymmetric keys in compliance with Health Insurance Portability and Accountability Act (HIPAA).[73] This encrypted anonymized information is sent for matching to the anonymized participant master index. While it is not possible to reverse the hash, source-specific tokens can be decrypted and re-encrypted so that records can be linked across sources. The result of the process is a unique anonymized identifier for each participant, which can be used to link participant records across sources (real world data and study data).

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is that this study will be performed in adult participants who will receive no direct benefit from participation in the study, except for participant reimbursement for the time and inconveniences that may arise from participation in the study. See Section 2.3 for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

Another ethical concern is the use of placebo vaccine and maintaining the study blind while the active study vaccine may prevent a serious disease. The study design, with continuous evaluation of efficacy, addresses that concern as much as possible. The sponsor will look into the possibility to offer the active study vaccine to placebo recipients, if VE is demonstrated, considering country-specific conditions, in accordance with local and national regulations and in consultation with the responsible national authorities. See Section 6.6 for details.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the US Department of Health and Human Services Office for Human Research Protections, and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period.[55,56]

In US only, for participants who consent to the optional collection of real-world medical data, the sponsor is committed to protect their data and privacy. Tokenization and matching procedures will be utilized to allow for those participant's medical data to be obtained without violation of participant confidentiality (See Section 4.2). Participants will be informed that consent to this part of the study is completely optional and that they can withdraw their consent at any given time. In case of withdrawal of consent, the sponsor will remove the token generated and any associated linked real-world data. Participation in or withdrawal from this optional part of the study will not affect the participation in the main study.

4.3. Justification for Dose

The dose level of Ad26.COV2.S to be assessed in the present study (5×10^{10} vp) is based on experience with other Ad26-vectored vaccines administered to adults in clinical studies including Ad26.ZEBOV (Ebola virus program); Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (HIV program); Ad26.CS.01 (malaria program); Ad26.RSV.FA2 and Ad26.RSV.preF (RSV program); and Ad26.ZIKV.001 (Zika virus program). Studies with Ad26.RSV.preF also included participants aged ≥60 years. The dose level of 5×10^{10} vp is the most extensively tested dose to date and has shown to be well tolerated and immunogenic in these vaccine programs. Safety data from studies with other Ad26-based vaccines are summarized in Section 2.3.1.

The same dose level is also being assessed in study VAC31518COV1001. Initial immunogenicity and safety data (28 days post dose 1 from Cohort 1a) from study VAC31518COV1001 has demonstrated that a single dose with the 5×10^{10} vp and 1×10^{11} vp Ad26.COV2.S dose levels is immunogenic (according to the study's prespecified criteria) and safe in adults ≥18-≤55 year of age. The sponsor has therefore decided to proceed with Ad26.COV2.S at a dose level of 5×10^{10} vp in the Phase 3 studies. Even though a single-dose regimen in study VAC31518COV1001 showed good immunogenicity that may already protect against COVID-19, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in a higher and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study. The single dose regimen will be further evaluated in study VAC31518COV3001.

Non-human primates immunized with a single-dose of Ad26.COV2.S (Study 20-14, dose level titration study) showed robust protection after intranasal and intratracheal challenge with SARS-CoV-2. Ad26.COV2.S at 5×10^{10} vp provided complete protection in the lung in 5 of 5 animals, and in 5 of 6 animals in the upper respiratory tract. All control animals showed substantial viral load in both the lower and upper respiratory tract.

The 5×10^{10} vp dose level will be assessed to determine whether Ad26.COV2.S has a similar immunogenicity profile to that observed with other Ad26-based vaccines.

4.4. End-of-study Definition

End-of-study Definition

The end-of-study is considered as the completion of the last visit for the last participant in the study. The final data from each participating study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed the assessments at the visit approximately 2 years after the last vaccination. Participants who prematurely discontinue study participation for any reason before completion of these assessments will not be considered to have completed the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within ≤28 days before randomization and 1st administration of the study vaccine, or on the day of the 1st vaccination. Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. Some inclusion and exclusion criteria only apply to a particular stage (1 or 2), as indicated below. See Section 4.1 for more details about enrollment in the different stages. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

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

1. Participants must provide consent indicating that he or she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.

2. Participant is willing and able to adhere to the prohibitions and restrictions specified in this protocol.

3. Criterion modified per Amendment 2

   3.1 Participant is ≥18 to <60 years or ≥60 years of age on the day of signing the ICF.

4. Criterion modified per Amendment 1:

   4.1 Criterion modified per Amendment 2:

   4.2 Criterion modified per Amendment 3:

   4.3 **Stage 1:** In the investigator's clinical judgement, participant must be either in good or stable health, including a BMI <30 kg/m^2.

Participants may have underlying illnesses (not associated with increased risk of progression to severe COVID-19[a,13] as specified in Exclusion Criterion 14), as long as their symptoms and signs are stable and well-controlled. If participants are on medication for a condition not part of the comorbidities listed in Exclusion Criterion 14, the medication dose cannot have been increased within 12 weeks preceding the 1st vaccination and expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and BMI at screening.

As of Stage 2: In the investigator's clinical judgement, participant may have a stable and well-controlled comorbidity including comorbidities associated with an increased risk of progression to severe COVID-19 as specified in Exclusion Criterion 14 (eg, stable/well-controlled HIV infection)*. If participants are on medication for a comorbidity (including comorbidities associated with an increased risk of progression to severe COVID-19), the medication dose cannot have been increased within 12 weeks preceding the 1st vaccination and must be expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and BMI at screening.

*Stable/well-controlled HIV infection includes:

a. CD4 cell count ≥300 cells/µL within 6 months prior to screening.

b. HIV viral load <50 copies/mL within 6 months prior to screening.

c. Participant must be on a stable anti-retroviral treatment (ART) for 6 months (unless the change is due to tolerability, in which case the regimen can be for only the previous 3 months; changes in formulation are allowed; nationwide guidelines that require transition from one ART regimen to another are allowed) and the participant must be willing to continue his/her ART throughout the study as directed by his/her local physician.

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

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

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

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

   Before randomization, participants must be either (as defined in Appendix 5):

[a]Per US CDC (Appendix 11). In this study, former or current smoking/vaping and mild hypertension (according to the Toxicity Grading Scale in Section 10.9) will not be considered as a comorbidity. In addition, for this study gestational diabetes was deleted from the list since it is not applicable as pregnant women are not allowed to participate in the study.

a. Not of childbearing potential

b. Of childbearing potential and practicing an acceptable effective method of contraception and agrees to remain on such a method of contraception from providing consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the 1st administration of study vaccine. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the 1st vaccination. Acceptable effective methods[a] for this study include:

   1. hormonal contraception:

      i. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

      ii. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)

   2. intrauterine device;

   3. intrauterine hormone-releasing system;

   4. bilateral tubal occlusion/ligation procedure;

   5. vasectomized partner (the vasectomized partner should be the sole partner for that participant);

   6. sexual abstinence*.

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

6. All participants of childbearing potential must:

   a. Have a negative highly sensitive urine pregnancy test at screening

   b. Have a negative highly sensitive urine pregnancy test on the day of and prior to each study vaccine administration.

7. Participant agrees to not donate bone marrow, blood, and blood products from the first study vaccine administration until 3 months after the last dose of the study vaccine.

8. Must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

9. Must be able to read, understand, and complete questionnaires in the eCOA (ie, the COVID-19 signs and symptoms surveillance question, the e-Diary, and the electronic patient-reported outcomes (ePROs) [see Appendix 1 for definition of terms]).

[a] Use of condoms is not considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms.[74]

5.2. Exclusion Criteria

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

1. Participant has a clinically significant acute illness (this does not include 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 1st dose of study vaccine; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.
2. Participant has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine; refer to the IB).
3. Criterion modified per Amendment 2:

   3.1 Participant has abnormal function of the immune system resulting from:

   a. Clinical conditions (eg, autoimmune disease or potential immune mediated disease or known or suspected immunodeficiency, or patient on hemodialysis) expected to have an impact on the immune response of the study vaccine. Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator. Non-immunomodulator treatment is allowed as well as steroids at a non-immunosuppressive dose or route of administration.

   b. Chronic or recurrent use of systemic corticosteroids within 6 months before administration of the 1st dose of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent.
   Note: Ocular, topical or inhaled steroids are allowed.

   c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of the 1st dose of study vaccine and during the study.
4. Criterion modified per Amendment 3:

   4.1 Participant received treatment with Ig in the 3 months or exogenous blood products (autologous blood transfusion are not exclusionary) in the 4 months before the planned administration of the 1st dose of study vaccine or has any plans to receive such treatment during the study.
5. Participant received or plans to receive:

   a. Licensed live attenuated vaccines – within 28 days before or after planned administration of the 1st or subsequent study vaccinations.

   b. Other licensed (not live) vaccines – within 14 days before or after planned administration of the 1st or subsequent study vaccinations.
6. Participant previously received a coronavirus vaccine.
7. Criterion modified per Amendment 1:

   7.1 Criteria modified per Amendment 2:

7.2 Participant received an investigational drug within 30 days (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational Ig or investigational 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 1st dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study. See also Section 6.8.

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

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

The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination (see also Exclusion Criterion 6) and during the study, except under the conditions described in Section 6.6.

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

    14.1 Criteria modified per Amendment 2:

14.2 Stage 1:

- Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19[a,13], ie, participants with moderate-to-severe asthma; chronic lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and

[a]Per US CDC (Appendix 11). In this study, former or current smoking/vaping and mild hypertension (according to the Toxicity Grading Scale in Section 10.9 will not be considered as a comorbidity. Gestational diabetes was deleted from the list since it is not applicable as pregnant women are not allowed to participate in the study.

pulmonary hypertension; moderate to severe high blood pressure; obesity (body mass index [BMI] ≥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; sleep apnea; and participants who live in nursing homes or long-term care facilities.

- Participants with a history of or current Parkinson's disease; seizures; ischemic strokes; intracranial hemorrhage; encephalopathy and meningoencephalitis.

15. **Stage 1:** Participant has a history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence).
16. Criterion modified per Amendment 2:

    16.1 Participant has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).

17. Criterion modified per Amendment 2:

    17.1 Participant had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before 1st vaccination, or will not have fully recovered from surgery requiring hospitalization, or has surgery requiring hospitalization planned during the time the participant is expected to participate in the study or within 6 months after the last study vaccine administration.

18. **Stage 1:** Participant has chronic active hepatitis B or hepatitis C infection per medical history.

Note: Investigators should ensure that all study enrollment criteria have been met prior to the 1st dose of study vaccine. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the 1st dose of study vaccine is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for retesting. The required documentation to support meeting the enrollment criteria is described under Source Documents in Appendix 3.

In areas where seroprevalence is predicted to be high, a screening serologic test for past or current infection with SARS-CoV-2 may be performed (in a local laboratory) at the discretion of the sponsor to restrict the proportion of seropositive participants in the study.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle considerations during the course of the study to be eligible for participation:

1. Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).

3. Agree to follow requirements for the electronic completion of the COVID-19 signs and symptoms surveillance question in the eCOA.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study, however, without referring to direct communication with participants. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

In cases where a participant does not meet the criteria for participation in this study (screen failure), the main reason for non-eligibility is to be documented in the eCRF.

An individual who does not meet the criteria for participation in Stage 1, but does meet the criteria for participation in Stage 2, will not be considered a screening failure and can be enrolled in the appropriate stage, if enrollment occurs within the 28-day Screening window.

An individual who does not meet the criteria for participation in this study (screen failure) or individuals for whom the 28-day screening window is exceeded may be rescreened on 1 occasion only.

All participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then re-start a new screening phase.

5.5. Criteria for Temporarily Delaying Administration of Study Vaccination

The following events constitute a temporary contraindication to study vaccination (Dose 1 and/or Dose 2):

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature ≥38.0°C/100.4°F) within 24 hours prior to the planned time of vaccination.
- An illness which in the judgement of the investigator may interfere with reactogenicity/Day 0-7 safety assessments.

If any of these events occur at the scheduled time for the 1st vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after

consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for the 2nd vaccination, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in the Schedules of Activities.

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1. Study Vaccines Administered

Ad26.COV2.S will be supplied at a concentration of 1×10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp. Placebo is 0.9% NaCl.

For blinding purposes, all participants will receive a vaccination at Day 1 and Day 57 (see Schedules of Activities), using the same volume (ie, 0.5 mL).

For information on vaccination windows, see Visit Windows in the Schedules of Activities. If a participant cannot be vaccinated within the allowed window (eg, if the window is missed due to a study pause [see Section 6.9]), the decision regarding vaccination will be assessed on a case-by-case basis, upon discussion between sponsor and investigator.

Study vaccine will be administered by IM injection into the deltoid muscle, preferably of the non-dominant arm. If an injection cannot be given in the deltoids due to a medical or other contraindication (for example, tattooed upper arms rendering it difficult to assess site reactogenicity), use alternative locations such as the hip, thigh or buttocks (to be avoided in overweight participants). In all circumstances, IM injections in other locations than the upper arm are not considered protocol deviations.

Study vaccine administration must be captured in the source documents and the eCRF.

Ad26.COV2.S will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[34]

Refer to the study site investigational product and procedures manual (SIPPM) and the Investigational Product Preparation Instructions (IPPI) for additional guidance on study vaccine administration.

Description of Interventions

Group Name	Group 1	Group 2
Intervention Name	Ad26.COV2.S (1×10^{11} vp/mL) (2 doses)	Placebo: 0.9% Sodium Chloride (2 doses)
Type	Biologic/vaccine (2 doses)	Placebo (2 doses)
Dose Formulation	Single-use vials, with an extractable volume of 0.5 mL	Single-use vials, with an extractable volume of 0.5 mL
Unit Dose Strength(s)	Ad26.COV2.S at a concentration of 1×10^{11} vp/mL (2 doses)	0.9% Sodium Chloride (2 doses)
Dosage Level(s)	**Day 1 and Day 57**: Ad26.COV2.S (5×10^{10} vp)	**Day 1 and Day 57:** Placebo
Route of Administration	IM injection	IM injection
Use	Experimental	Placebo-comparator
Investigational Medicinal Product (IMP)	Yes	No
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	Yes
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	The study vaccines will be packaged and labeled according to good manufacturing practices and local regulations. The study vaccines will not be packed in individual participant kits, 1 kit will be used by multiple participants. Each kit will contain single-use vials.	
	Not in child resistant packaging	

IM = intramuscular ; vp = virus particles

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study vaccine must be stored in a secured location with no access for unauthorized personnel and at controlled temperatures as indicated on the clinical labels. If study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected supplies can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

Refer to the study SIPPM and the IPPI for additional guidance on study vaccine preparation, handling, and storage.

An unblinded study-site pharmacist, or other qualified individual, who will have no other study function following vaccination, will prepare the appropriate vials and syringes, labeled with the participant's identification number, and provide the syringes for the study vaccine in a blinded manner to the blinded vaccine administrator (a trained and qualified study nurse, medical doctor, otherwise qualified healthcare professional) who will perform the injection.

Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study vaccine containers.

Study vaccine must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's unblinded site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the vaccine accountability form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine accountability form.

Potentially hazardous materials containing hazardous liquids, such as needles and syringes should be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be administered only to participants participating in the study. Returned study vaccine must not be dispensed again, even to the same participant. Study vaccine may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study vaccine are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 vaccination groups (active vaccine [Group 1] versus placebo [Group 2]). This will be based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by vaccination unit (eg, site, mobile unit), age group (≥18 to <60 years of age versus ≥60 years of age), and absence/presence of comorbidities that are or might be associated with an increased risk of progression to severe COVID-19 as described in Exclusion Criterion 14.

The IWRS will assign a unique intervention code, which will dictate the intervention assignment for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

Blinding will be guaranteed by the preparation of the study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation and dispensing, and by the administration of vaccine in a masked syringe by a blinded study vaccine administrator. Participants will be randomly assigned to 1 of the groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor and using the IWRS.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the study vaccine assignment (ie, immunogenicity data, study vaccine accountability data, study vaccine allocation, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. Note that key personnel of the sponsor will be unblinded at the time of primary analysis. Sites and participants will remain blinded until all participants have completed the study. Details will be provided in the IDMC Charter. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible,

to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IWRS and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations. Participants should not be allowed to receive further study vaccinations and are only to be followed for safety evaluation visits.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

Investigators may receive requests to unblind study participants who become eligible to receive an authorized/licensed COVID-19 vaccine if/when these become available. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorized/licensed vaccine according to local immunization guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures described above. The reason for the unblinding request should be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see Section 6.8).

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. In the event the participant is unblinded, no further study vaccination will be permitted. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the Schedules of Activities to the extent that they permit. Safety, efficacy, and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, including participants in the safety subset, if applicable and feasible. All data will be analyzed separately from the point of unblinding for safety, efficacy and immunogenicity, as described in the Statistical Analysis Plan.

6.4. Study Vaccine Compliance

Study vaccines will be administered intramuscularly by a study vaccine administrator – a trained and qualified study nurse, medical doctor, otherwise qualified HCP. The date and time of each study vaccine administration and the location used will be recorded in the eCRF.

6.5. Dose Modification

Dose modification is not applicable in this study.

6.6. Continued Access to Study Vaccine After the End of the Study

At the end of the study, participants who received placebo may be offered the Ad26.COV2.S study vaccine at no cost when the vaccine has been shown to be safe and efficacious, and preferably also after the duration of protection has been determined. This will occur in accordance with local and national regulations and in consultation with the responsible national authorities. The consent form will inform all potential volunteers that this is our intent, if feasible.

If the Ad26.COV2.S study vaccine is determined to be efficacious during the course of this study, the country-specific conditions (eg, registration status and local recommendations/regulations), ethical considerations, requirements for duration of protection, and long-term safety will determine whether the study vaccine can be made available to vaccinate the placebo group, at the time of this occurrence. This will be done by an amendment to the study, which will further outline study conditions and options for each participant.

At the time when a COVID-19 vaccine is determined to be efficacious and authorized/licensed for use, some participants may become eligible to receive such a vaccine, depending on country-specific conditions (eg registration status, local recommendations/regulations, vaccine availability or the specific target group for vaccination). The investigator will discuss with the participants the available information and options to allow the participant to make an informed choice as to whether they qualify to receive the authorized/licensed vaccine and whether they should request individual unblinding to take up the offer of an authorized/licensed COVID-19 vaccine. In the event the participant is unblinded, no further study vaccination will be permitted. Safety evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. All data will be analyzed separately from the point of unblinding for safety, efficacy and immunogenicity (under the conditions outlined in Section 6.3), as described in the SAP.

6.7. Treatment of Overdose

For this study, any dose of Ad26.COV2.S greater than the assigned dose will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of a known overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AE/SAE/MAAE (ie, the participant will remain at the study site for at least 1 hour and will be closely monitored for allergic or other reactions by study staff. Follow-up telephone calls 12 hours and 24 hours post-dose will be made).
- Document the quantity of the excess dose in the source document.
- Report as a special reporting situation.

6.8. Prestudy and Concomitant Therapy

Prestudy therapies are only to be recorded for participants with relevant comorbidities and participants aged ≥60 years. For these participants, all prestudy therapies (excluding vitamins,

herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, and exercise regimens) administered up to 30 days before the 1st vaccination must be recorded at screening.

For all participants, concomitant therapies associated with an SAE meeting the criteria outlined in Section 10.4.1 will be collected and recorded in the eCRF from the moment of 1st vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of 1st vaccination until 6 months after the last vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study.

For all participants, concomitant therapies associated with COVID-19 will be captured in the electronic eCRF for the duration of the study.

For participants in the Safety Subset, concomitant therapies associated with unsolicited AEs will be collected and recorded in the eCRF from the time of 1st vaccination through 28 days after the last vaccination. Concomitant therapies associated with solicited AEs will be collected by the participants and recorded in the eCRF from the time of each vaccination through 7 days after each vaccination. If the solicited signs and symptoms are not resolved by 7 days post-vaccination, the concomitant therapies associated with these solicited AEs will be collected by the participants and recorded in the eCRF until Day 29 post-vaccination or until they are resolved, whichever comes first.

Antipyretics are recommended post-vaccination for symptom relief as needed. Prophylactic antipyretic use is not encouraged; however, in some instances, it could be considered for participants with special circumstances and/or comorbidities.

Participants may not have received an investigational drug within 30 days (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational Ig or investigational 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 1st dose of the study vaccine. During the study, the use of investigational vaccines other than the study vaccine is not allowed, and the use of investigational drugs is only allowed if medically indicated. Treatment with investigational COVID-19 drugs after diagnosis of a COVID-19 case is allowed during the follow-up period and needs to be recorded in the COVID-19 episode description.

Licensed live attenuated vaccines should be given at least 28 days before or at least 28 days after a study vaccination. Other licensed (not live) vaccines (eg, influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given more than 14 days before (or more than 14 days after, as per Exclusion Criterion 6) administration of any dose of the study vaccine in order to avoid potential confusion of adverse reactions and potential immune interference. The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination and during the study except under the conditions described in Section 6.6. If a vaccine

is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Chronic or recurrent use of systemic corticosteroids[a] at immunosuppressive dose and administration of antineoplastic and immunomodulating agents or radiotherapy are prohibited during the study and within 6 months before the planned administration of the 1st dose of the study vaccine. If any of these agents are indicated in a disease setting, these must take priority over the study vaccine.

Refer to Section 5.2 for further details of prohibited therapy.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. The participant should remain in the study but receive no further study vaccination. Depending on the time of the occurrence, any participant who receives a prohibited concomitant therapy will not be included in the immunogenicity analyses.

6.9. Study Vaccination Pausing Rules for Stage 1

The sponsor (including designated sponsor teams) and/or Sponsor Committee as well as the investigator(s) will monitor safety in a blinded manner. Adverse events that may lead to the study vaccination pausing rules (applicable to Stage 1 only) are described below and will be assessed by the designated sponsor team/committee to confirm that the study pause is warranted.

The occurrence of any of the following events in Stage 1 will lead to a pause in further study vaccination:

1. Death of a participant, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded; OR

2. One or more participants experience an SAE (solicited or unsolicited) that is determined to be related to study vaccine; OR

3. One or more participants experience anaphylaxis or generalized urticaria, clearly not attributable to other causes than vaccination with study vaccine.

To enable prompt response to a situation that could trigger pausing rules, the investigator should notify the sponsor's medical monitor or designee (AND fax or email the SAE form to Global Medical Safety Operations, if applicable), immediately and no later than 24 hours after becoming aware of any related SAE AND update the eCRF with relevant information on the same day the SAE information is collected (see also Section 8.3.1). Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted and informs the IDMC of the decision. All sites will be notified immediately in the event of a study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of IDMC members and coordination of an IDMC meeting in the event of a study pause.

[a] Note: Ocular, topical or inhaled steroids are allowed.

The IDMC will review unblinded data and will make recommendations regarding the continuation of the study to the sponsor study team. Resumption of vaccinations will start only upon receipt of written recommendations by the IDMC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. The formal recommendation from the IDMC will be forwarded by the investigator to the IRB/IEC and by the sponsor to the relevant health authorities, according to local standards and regulations. Refer to Section 10.3.6, Committees Structure in Appendix 3.

Vaccinations for an individual participant may be suspended for safety concerns other than those described in the pausing criteria, at the discretion of the investigator if he/she feels the participant's safety may be threatened. The sponsor's medical monitor or designee or the investigator(s) (upon consultation with the sponsor's medical monitor or designee) may initiate IDMC review for any single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

Vaccinations for the study may be suspended for safety concerns other than those described above, or before pausing rules are met, if, in the judgement of the IDMC, participant safety may be threatened.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Study vaccinations will be withheld for the reasons listed below. These participants must not receive any further doses of study vaccine but should remain on study for follow-up with assessments of safety, efficacy, and immunogenicity as indicated in the Schedules of Activities. Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Unblinding of a study participant in order to receive an authorized/licensed COVID-19 vaccine
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic or recurrent use of systemic corticosteroids and administration of antineoplastic and immunomodulating agents or radiotherapy
- Participant receives any experimental medication (including experimental vaccines other than the study vaccine) or receives an anti-COVID-19 vaccine or treatment

- Withdrawal of consent to receive further study vaccination
- Participant has a molecularly confirmed SARS-CoV-2 infection based on samples collected within the study (see Section 8.1.2).

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent from the study
- Death
- Repeated failure to comply with protocol requirements

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3.5 in Appendix 3). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedules of Activities summarize the frequency and timing of all measurements applicable to this study.

All participants will be provided access to an eCOA digital tool. This eCOA will be used to collect COVID-19 signs and symptoms surveillance info for all participants, ePRO (Symptoms of infection with Coronavirus-19 [SIC], including body temperature, and pulse oximetry results) for all participants at baseline and in case of COVID-19-like signs and symptoms, and e-Diary data on 7-day reactogenicity (solicited signs and symptoms, including body temperature) in the Safety Subset. All eCOA assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of ePROs.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: vital signs before blood draws. If needed, assessments may be performed on another day within the applicable visit window. Actual dates and times of assessments will be recorded in the source document, the eCRF, or the sample requisition form.

All participants will be provided a thermometer to measure body temperature if they experience COVID-19-like signs and symptoms. Participants in the Safety Subset will be provided a ruler (to measure local injection site reactions) and a participant e-Diary in the eCOA digital tool to record body temperature and solicited local (at injection site) and systemic signs and symptoms. The e-Diary includes instructions on how to capture the data and grading scales to assess severity of the signs and symptoms post-vaccination (reactogenicity). The study staff is responsible for providing appropriate training to the participant to avoid missing or incorrect data. The e-Diary will be reviewed by the study personnel at visits indicated in the Schedules of Activities. If the e-Diary review is missed, the diary will be reviewed during the following visit.

All participants will also be provided with a kit to collect nasal swabs samples and recipients to collect saliva (see Section 8.1.2).

The total blood volume to be collected over the course of the study from each participant will be approximately 120.0 mL for participants in the Immunogenicity Subset and 40.0 mL for the other participants. Additional blood samples (up to 30 mL) will be collected from participants that experience COVID-19-like signs and symptoms meeting prespecified criteria for suspected COVID-19. Refer to the Schedules of Activities for the total blood volume (serum and, as applicable, whole blood samples) to be collected at each visit, over the complete course of the study, and in the event of a suspected COVID-19 episode. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

If allowed by local regulation, study visits may take place at the participant's home or other location in the event of ongoing SARS-CoV-2 transmission in the area of the participant.

If possible and allowed per local regulation, visits, except screening and vaccination visits, can be performed by a phone call or a telemedicine contact provided that assessments requiring a face-to-face interaction between the participant and a trained health care professional (including but not limited to blood sampling) are performed by a Site staff member or a designee at the participant's home or other location, whichever is applicable. Conversely, in case of home visit, assessments that cannot be delegated to a designee must be performed by an appropriate Site staff member via a phone call or telemedicine.

Visit Windows

Visit windows are provided in the Schedules of Activities. The participant should be encouraged to come on the exact day planned and use the visit window only if absolutely necessary.

If a vaccination window is missed due to a study pause (see Section 6.9), efforts will be made to still vaccinate the participant as soon as possible after the pause has been lifted, even if out of window. The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination. If a participant misses a vaccination, the post-vaccination visits will be calculated from the imputative vaccination date according to protocol.

Screening

The study will consist of a screening phase of up to 28 days. Screening may also be performed prior to randomization on the day of vaccination. In that case, Visits 1 and 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and 1st vaccination.

Screening may be conducted in part via a sponsor- and IRB/IEC-pre-approved non-study-specific screening consent process, but only if the relevant pre-screening tests are identical to the per-protocol screening tests and are within 28 days prior to the 1st vaccination. However, no study-specific procedures, other than these pre-approved pre-screening assessments, will be performed until the participant has signed the study-specific ICF. The study-specific ICF date will be collected for the study database. The non-study-specific ICF will be considered source data.

Long term follow-up

Until 1 year after the 2nd vaccination, each participant will be asked at least twice a week, through the eCOA, if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. As of 1 year after the 2nd vaccination, until the end of the 2-year follow-up period, the frequency of this (suspected) COVID-19 surveillance (symptom check) through the eCOA will decrease to once every 2 weeks. All participants will be monitored for safety (including enhanced disease) for 2 years after the last vaccination, ie, until the last study visit. Sites should monitor participant compliance with (suspected) COVID-19 surveillance (symptom check) and SIC completion on a daily basis and reach out to a participant if the participant fails to complete the surveillance question upon any of these reminders. Every effort will be made to document the status of all participants that are lost to follow-up due to not completing the eCOA and for whom hospitalization has not been recorded. The questionnaire will be accessible on the eCOA platform in between scheduled reminders and participants will be encouraged to answer the surveillance question in the eCOA as soon as possible after the onset of COVID-19-like symptoms. Procedures to be followed in case of (suspected) COVID-19 are outlined in Section 8.1.2.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Schedules of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for Ad26.COV2.S
- Thermometer
- Ruler (to measure diameter of any erythema and swelling)
- A pulse oximeter
- Pharmacy manual/SIPPM
- IPPI
- IWRS Manual
- Sample ICF
- Laboratory manual and laboratory supplies
- Nasal swab kits, saliva recipients, and participant instructions

- eCOA platform access and participant instructions. Participants may use their own eDevice using an application if their device (smartphone or tablet) is compatible, or a web portal. Provisioned devices will be available on a limited basis.
- Tablet for eConsent, if applicable
- Contact information page(s)
- eCRF completion guidelines

8.1. Efficacy and Immunogenicity Assessments

No generally accepted immunological correlate of protection has been demonstrated for SARS-CoV-2 to date.

8.1.1. Prespecified Criteria for Suspected COVID-19

The criteria for suspected COVID-19 (ie, the triggers to proceed with home-collection of the nasal swabs on COVID-19 Day 1-2 and to proceed with the COVID-19 Day 3-5 visit) are prespecified as follows:

- **A positive RT-PCR result for SARS-CoV-2, through a private or public laboratory independent of the study, whether symptomatic or asymptomatic**

  OR

- **New onset or worsening of any 1 of the symptoms listed below, which lasts for at least 24 hours, not otherwise explained:**
  - Headache
  - Malaise (appetite loss, generally unwell, fatigue, physical weakness)
  - Myalgia (muscle pain)
  - Chest congestion
  - Cough
  - Runny nose
  - Shortness of breath or difficulty breathing (resting or on exertion)
  - Sore throat
  - Wheezing
  - Eye irritation or discharge
  - Chills
  - Fever (≥38.0°C or ≥100.4°F)
  - Pulse oximetry value ≤95%, which is a decrease from baseline
  - Heart rate ≥90 beats/minute at rest, which is an increase from baseline
  - Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)

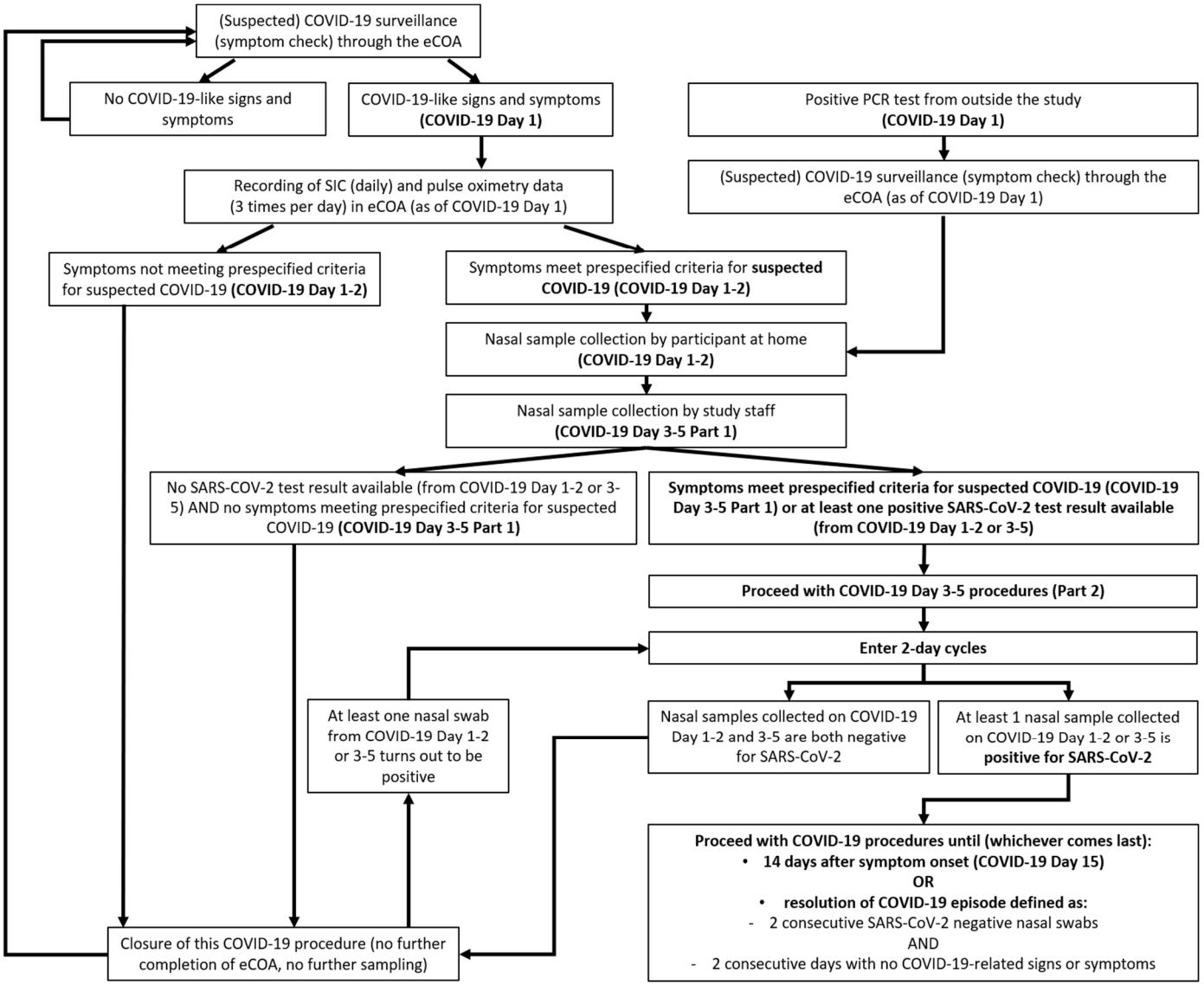
- Neurologic symptoms (numbness, difficulty forming or understanding speech)
- Red or bruised looking toes
- Skin rash
- Taste loss or new/changing sense of smell
- Symptoms of blood clots: pain/cramping, swelling or redness in your legs/calves
- Confusion
- Bluish lips or face
- Clinical suspicion/judgement by investigator of symptoms suggestive for COVID-19

As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19.

8.1.2. Procedures in the Event of (Suspected) COVID-19

Procedures to be performed in the event a participant experiences signs or symptoms suggesting possible COVID-19 or a participant became aware of a positive RT-PCR test result for SARS-CoV-2 outside the study context, whether symptomatic or asymptomatic, are detailed in the Schedules of Activities. A high-level schematic overview is presented in Figure 2.

Figure 2: Decision Tree for COVID-19 Procedures



COVID-19 = coronavirus disease-2019; eCOA = electronic clinical outcome assessment; PCR= polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19.

For all medical visits for COVID-19 or COVID-19 complications, including those resulting in hospitalization, a standard list of questions will be provided (MA-COV form [Appendix 8]), with the aim to collect additional information on any other diagnostics (eg, chest X-rays, spirometry, pulmonary function tests) or interventions during the clinical course of COVID-19. The MA-COV form will be provided to the participant at the first vaccination visit and should be completed by the medical care provider or the study site personnel during medical visits for COVID-19 or COVID-19 complications.

Note: if for any reason a site visit per the procedures described below is not feasible, a member of the study staff or designee can visit the participant at home (or at the hospital or other location, if needed), if allowed by local regulations.

Day 1-2 procedures in case of signs and symptoms

If a participant records in the eCOA or informs the site that he/she experienced any signs or symptoms suggesting possible COVID-19, this will be considered **COVID-19 Day 1** (day of onset of signs and symptoms). The participant will be asked to complete the ePROs (ie, the SIC [Appendix 6], including body temperature) in the eCOA.

Notes:

- The SIC questionnaire asks the participant if he/she had any of the prespecified signs or symptoms (see Appendix 6) during the past 24 hours, and (when applicable) to rate the severity. The SIC questionnaire takes approximately 5 minutes to complete.
- The participant should record the highest temperature in the last 24 hours in the SIC.
- The participant should record at least 1 of the 3 pulse oximetry readings in the last 24 hours in the eCOA.
- If a participant is unable to complete the SIC in the eCOA, a study staff member can collect information on the participant's symptoms and body temperature, by contacting the participant by telephone (or visit the participant at home), reading the questions aloud to the participant and entering the participant's responses on the participant's behalf. If the participant requires assistance, the participant's caregiver can help the participant to complete the SIC in the eCOA by reading the questions aloud to the participant and recording the participant's responses in the eCOA using the caregiver's unique identifier and PIN on the participant's behalf. Procedures for caregivers to collect and report the participant's responses to the eCOA questions will be detailed in instructions for caregiver assessment of COVID-19 episodes. Details are provided in the PRO completion guidelines.

Based on the information collected through the SIC, the site will reach out to the participant at the latest on COVID-19 Day 2 (the day after the day of symptom onset) to assess whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.1). As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19. If the participant would actively reach out to the site already on COVID-19 Day 1, the site should already make a first assessment on COVID-19 Day 1 to check whether the reported signs and symptoms qualify as a suspected COVID-19

episode using prespecified criteria (Section 8.1.1). As soon as the prespecified criteria for suspected COVID-19 are met (**COVID-19 Day 1-2**), the participant will be asked to undertake the COVID-19 procedures. In particular:

- The participant will be asked to continue to complete the ePROs in the eCOA, as specified above for COVID-19 Day 1:
  - SIC (including body temperature): every day, preferably in the evening around the same time each day.
  - Blood oxygen saturation and pulse rate using a pulse oximeter 3 times a day, preferably in the morning, at lunch time, and in the evening.

    Note: the ePROs do not have to be completed if special circumstances occur, such as hospitalization or ventilation, in which case the reason for not completing the ePROs should be recorded by site staff in the eCRF.
- The participant will be asked to collect a nasal swab at home on **COVID-19 Day 1-2**, as soon as possible after it has been confirmed that the prespecified criteria for suspected COVID-19 are met. If the participant requires assistance, a trained HCP can help the participant to collect the nasal swab. The study site should arrange transfer of the nasal swab to the study site as soon as possible after collection, preferably within 24 hours. The COVID-19 Day 1-2 nasal swab can also be collected at the study site (or hospital or other location, if needed), if preferred by the participant.

Day 1-2 procedures in case of a positive RT-PCR test outside the study context

If a participant becomes aware of a positive RT-PCR test for SARS-CoV-2, he/she should contact the site as soon as possible. The day the participant became aware of the positive PCR test will be considered COVID-19 Day 1. Regardless of whether the participant is symptomatic or asymptomatic, he/she will be asked to:

- Complete the (suspected) COVID-19 surveillance (symptom check) in the eCOA. In case of COVID-like signs and symptoms, they will need to complete the SIC (Appendix 6, including body temperature) in the eCOA.
- Collect a nasal swab at home on COVID-19 Day 1-2, as described for the participants with signs and symptoms (see above).

These precautionary measures are to ensure that site staff who come into physical contact with a participant deemed to be a COVID-19 case undertake the proper safety procedures such as wearing of personal protective equipment.

Day 3-5 procedures for all participants who have met the prespecified criteria for (suspected) COVID-19

The participant will be asked to come to the site on **COVID-19 Day 3-5** (between 2 and 4 days after symptom onset/becoming aware of a positive RT-PCR test).

- If a site visit is not feasible, a member of the study staff or designee could visit the participant at home (or at the hospital or other location, if needed), if allowed by local regulations. The

study staff or designee visiting participants at home will use personal protective equipment according to local regulations. The COVID-19 Day 3-5 assessments may also be performed by a trained HCP, if allowed per local regulations.

- During **Part 1** of the **COVID-19 Day 3-5** visit, if the participant has experienced COVID-19 like signs and symptoms, the site will interview the participant to assess whether the reported signs and symptoms still qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.1). In addition, for all participants, a qualified member of the study site will measure vital signs (body temperature, blood pressure, heart rate, and respiratory rate) and pulse oximetry. A targeted physical examination will be performed based on the judgement of the investigator. A nasal swab will be collected for detection of SARS-CoV-2 by a qualified member of the study site.
- If the signs and symptoms still meet the prespecified criteria for suspected COVID-19 on COVID-19 Day 3-5 or if the nasal sample collected at Day 1-2 or Day 3-5 visits is positive for SARS-CoV-2 (tested by RT-PCR), the following assessments and procedures are to be performed during **Part 2** of the **COVID-19 Day 3-5** visit: a blood sample for sero-confirmation of SARS-CoV-2 infection will be collected by a qualified member of the study site. A saliva sample will be taken by the participant during the study visit. The MRU questionnaire will be completed based on a clinical interview (Appendix 7). The medical history and description of COVID-19 episode will be collected by interview with the participant.
- If allowed by local regulations and if the participant consents, he/she will be interviewed on characteristics related to their current work situation, living situation, and community interactions (See Appendix 12). These data will be used for risk factor analysis.
- If the signs and symptoms no longer meet the prespecified criteria for suspected COVID-19 on COVID-19 Day 3-5 and no result from nasal swabs collected on Day 1-2 or Day 3-5 visits is available, the participant will not undertake any further COVID-19 procedures. He/she will fall back to the default Schedules of Activities, until the end of the study/early withdrawal.

Procedures during the 2-day cycles

If a participant has signs and symptoms that meet the prespecified criteria for suspected COVID-19 (Section 8.1.1) at COVID-19 Day 3-5 visit or has at least one positive sample for SARS-CoV-2 collected on COVID-19 Day 1-2 or Day 3-5 visits, he or she will be asked to undertake the COVID-19 procedures, in particular:

- All participants will be asked to collect a nasal swab and a saliva sample at home once every 2 days (daily alternating between nasal swabs and saliva samples). If the participant requires assistance, a trained HCP can help the participant to collect the nasal swabs and/or saliva samples. The study site should arrange transfer of the nasal swabs and saliva samples to the study site within 3 days after collection. Details are provided in the laboratory manual.
- In case of signs and symptoms: The participant will be reminded to further complete the ePROs in the eCOA as described for COVID Day 1-2.
- In case the nasal swabs collected on Day 1-2 or Day 3-5 visits are tested positive for SARS-CoV-2 and the participant is asymptomatic: the participant will be reminded to further complete (suspected) COVID-19 surveillance (symptom check).

- If, on COVID-19 Day 3-5, the participant stopped the COVID-19 procedures and returned to default Schedules of Activities, due to lack of signs and symptoms and unavailability of results from nasal swabs collected on Day 1-2 and Day 3-5 visits, the participant will be contacted as soon as at least one of these samples is found to be positive for SARS-CoV-2 presence. The participant will be asked to resume COVID-19 procedures, until 14 days after symptom onset (COVID-19 Day 15) or until **resolution of the COVID-19 episode**, whichever comes last.

  Note:

  - Participants should be encouraged by the site to collect nasal swabs and saliva samples as indicated in the Schedules of Activities. If the participant is unable or unwilling to collect all samples as requested, the participant should still complete the other COVID-19 assessments, including the visit at COVID-19 Day 29.

Day 29 procedures

If a participant has at least 1 SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1-2 or Day 3-5 visits, then he or she will be asked to return to the site on COVID-19 Day 29 (±7 days) where a blood sample will be drawn for sero-confirmation of SARS-COV-2 infection (antibody). A qualified member of the study site will measure vital signs (body temperature, blood pressure, heart rate, and respiratory rate) and pulse oximetry. A targeted physical examination will be performed based on the judgement of the investigator. The MRU questionnaire will be completed based on a clinical interview (Appendix 7). The medical history and description of COVID-19 episode will be collected by interview with the participant. If the participant is still symptomatic, he/she will complete the SIC (Appendix 6) in the eCOA. Asymptomatic participants will complete the (suspected) COVID-19 surveillance (symptom check).

Note: The COVID-19 Day 29 assessments may also be performed by a trained HCP at the participant's home, if allowed per local regulations.

This visit can be combined with a regular study visit if within the applicable visit windows.

Closure of the COVID-19 episode

The participant should continue the COVID-19 procedures until any of the following occurs, based on molecular test results:

- If both nasal swabs (collected on COVID-19 Day 1-2 and COVID-19 Day 3-5) are **negative** for SARS-CoV-2, the participant will not undertake any further COVID-19 procedures and will fall back to the default Schedules of Activities, until the end of the study/early withdrawal.
- If the participant has at least 1 SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1-2 or Day 3-5 visits, then the participant will be asked to undertake the COVID-19 procedures (2-day cycles) until 14 days after symptom onset (COVID-19 Day 15) or until **resolution of the COVID-19 episode**, whichever comes last[a]. Resolution of the COVID-19 episode is defined as having 2 consecutive SARS-CoV-2 negative nasal swabs and 2 consecutive days with no COVID-19-related signs or symptoms. Once past COVID-19 Day 15, participants

[a] long-term sequelae of COVID-19 will not be followed until their resolution

should stop the collection of nasal swabs and saliva samples as soon as 2 consecutive nasal swabs are SARS-CoV-2 negative, but (if still symptomatic at that time) should continue completing the ePROs (including SIC, body temperature, and pulse oximetry) in the eCOA until 2 consecutive days with no COVID-19-related signs or symptoms.

Note: for participants who have signs and symptoms present at baseline (assessed pre-vaccination), only signs and symptoms that are associated with COVID-19 and that developed during the COVID-19 episode are to be taken into account.

Upon closure of the COVID-19 episode and procedures, all participants will fall back to the default Schedules of Activities, until the end of the study/early withdrawal.

All confirmed COVID-19 episodes will be communicated to the respective participant and to other authorities according to local regulations.

If the participant experiences new signs or symptoms suggesting possible COVID-19 at a later point in time, the participant would re-start the COVID-19 procedures from COVID-19 Day 1 onwards.

With regards to the ePRO (ie, the SIC, including body temperature):

- The ePRO instrument will be provided in the local language in accordance with local guidelines.
- The ePRO instrument must be available for regulators and for IRB/ERC submissions, therefore the ePRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol.
- The ePRO and AE data will not be reconciled with 1 another.

8.1.3. Efficacy Assessments

Identification and molecular confirmation of SARS-CoV-2 infection and symptomatic COVID-19 will be performed throughout the study as described in Section 8.1.2. The ePRO to evaluate VE parameters will be the SIC. See Section 8.1.3.1 for Case Definition of Moderate to Severe/Critical COVID-19 and Section 8.1.3.2 for Case Definition of Mild COVID-19.

Molecular confirmation of SARS-CoV-2 infection by a central laboratory will be used for the analysis of the case definition.

The severity of all COVID-19 cases will be assessed using the case definitions and will be independently evaluated by a CEC (see Section 8.1.3.6). Classification of severity will be based on the highest degree of severity during the observation period (see Sections 8.1.3.1 and 8.1.3.2).

The occurrence of COVID-19-related hospitalization and COVID-19-related complications (such as but not limited to hyperinflammatory syndrome, pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death)[62] will be monitored throughout the study.

As a secondary objective, VE in the prevention of asymptomatic SARS-CoV-2 infection and mild COVID-19 will be analyzed. An immunologic test for SARS-CoV-2 seroconversion (ELISA

and/or SARS-CoV-2 immunoglobulin assay) based on SARS-CoV-2 N protein, will be performed to identify cases of asymptomatic infection. This assay will be performed on samples obtained at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination (see Section 8.1.3.5).

8.1.3.1. Case Definition for Moderate to Severe/Critical COVID-19

For the primary -endpoint (see Section 3), all moderate and severe/critical COVID-19 cases will be considered.

Case Definition for Moderate COVID-19

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

AND at any time during the course of observation[a]:

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

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

OR

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

- Fever (≥38.0°C or ≥100.4°F)
- Heart rate ≥90 beats/minute
- Shaking chills or rigors
- Sore throat
- Cough
- Malaise as evidenced by 1 or more of the following**:
  - Loss of appetite
  - Generally unwell
  - Fatigue
  - Physical weakness
- Headache
- Muscle pain (myalgia)
- Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)**
- New or changing olfactory or taste disorders
- Red or bruised looking feet or toes

* SpO_2 criteria will be adjusted according to altitude, per the investigator judgement.

** Having 2 or more elements of a symptom (eg, vomiting and diarrhea or fatigue and loss of appetite) is counted only as 1 symptom for the case definition. To meet the case definition, a participant would need to have at least 2 different symptoms.

[a] Participants will be asked to undertake the COVID-19 procedures until 14 days after symptom onset (COVID-19 Day 15) or until **resolution of the COVID-19 episode**, whichever comes last (see Section 8.1.2).

Case Definition for Severe/Critical COVID-19

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

AND any 1 of the following at any time during the course of observation[a]:

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

  * SpO_2 criteria will be adjusted according to altitude per the investigator judgement.
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to the ICU
- Death

8.1.3.2. Case Definition for Mild COVID-19

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

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

A case is considered mild when it meets the above case definition but not the moderate to severe/critical definition in Section 8.1.3.1.

8.1.3.3. US FDA Harmonized Case Definition for COVID-19

If a participant presents with symptoms as those listed by the US FDA harmonized case definition[11] (see Appendix 10), the investigator (or designated medically trained clinician) should assess if these are suggestive of COVID-19:

[a] Participants will be asked to undertake the COVID-19 procedures until 14 days after symptom onset (COVID-19 Day 15) or until **resolution of the COVID-19 episode**, whichever comes last (see Section 8.1.2).

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample; **AND**
- COVID-19 symptoms consistent with those defined by the US FDA harmonized case definition[11] at the time of finalization of this protocol: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.

8.1.3.4. Case Definition for Asymptomatic or Undetected COVID-19

If a participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms (see Section 8.1.1),

AND

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

OR

- develops a positive serology (non-S protein) test

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

A molecularly confirmed positive RT-PCR for SARS-CoV-2 will need to be captured in the eCRF.

8.1.3.5. SARS-CoV-2 Seroconversion Assessment

An immunologic test for SARS-CoV-2 seroconversion (ELISA and/or SARS-CoV-2 immunoglobulin assay) based on SARS-CoV-2 N protein, will be performed to identify cases of asymptomatic infection on samples obtained at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination (see Section 8.1.4).

8.1.3.6. Clinical Evaluation Committee

In addition to the specific case definitions, described in Sections 8.1.3.1 and 8.1.3.2, a blinded CEC will be established to evaluate the diagnosis, severity, classification, and duration of each identified COVID-19 case in the study. This committee is not an endpoint adjudication committee but will independently evaluate the severity of the COVID-19 cases. A comparison between the official case definition endpoint and CEC evaluation will be made. The CEC will consist of independent clinical infectious disease experts and a pulmonologist. The CEC deliberations per case and conclusions will be documented by the CEC and will be provided to the sponsor.

8.1.4. Immunogenicity Assessments

Blood will be collected from all non-Immunogenicity Subset participants for humoral immunogenicity assessments at Day 1 (before the 1st vaccination), 14 days, 6 months, and 1 year after the 2nd vaccination.

For a total of approximately 400 participants in the Immunogenicity Subset (ie, participants at sites with access to appropriate processing facilities), blood will be collected for analysis of humoral immune responses before each vaccination, 28 days after the 1st vaccination and 14 days , 6 months, 1 year, 18 months, and 2 years after the 2nd vaccination.

All participants in the Immunogenicity Subset will be enrolled from Study Stage 2. Participants in the Immunogenicity Subset will be divided into 4 groups as presented in Table 2.

Table 2: Sample Size and Distribution of the Immunogenicity Subset Between Active and Placebo Groups

Study Vaccine	Subset 1a	Subset 1b	Subset 2a	Subset 2b
5×10^{10} vp/5×10^{10} vp	50	50	50	50
Placebo/placebo	50	50	50	50
Total	**100**	**100**	**100**	**100**

vp = virus particles
Subset 1a: healthy participants ≥18 years to <60 years of age without relevant comorbidities, enrolled during Stage 2.
Subset 1b: healthy participants ≥60 years of age without relevant comorbidities, enrolled during Stage 2.
Subset 2a: participants ≥18 to <60 years of age with relevant comorbidities, enrolled during Stage 2.
Subset 2b: participants ≥60 years of age with relevant comorbidities, enrolled during Stage 2

During a COVID-19 episode, blood will be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 for immunogenicity assessments, including the assays summarized in Table 3.

Table 3: Immunogenicity Assays

Humoral Assays	Purpose
Supportive of Secondary Objectives	
SARS-CoV-2 binding antibodies to S protein (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
SARS-CoV-2 seroconversion based on antibodies to N protein (ELISA and/or SARS-CoV-2 immunoglobulin assay)	Analysis of antibodies binding to SARS-CoV-2 N protein
Supportive of Exploratory Objectives	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus, and/or pseudovirion expressing S protein
SARS-CoV-2 binding antibodies to S protein (MSD)	Analysis of antibodies binding to SARS-CoV-2 S protein (different than the assays supportive of the secondary objectives) and the receptor-binding domain (RBD) of SARS-CoV-2 S protein
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire
Adenovirus neutralization (VNA)	Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector
Binding antibodies to other coronaviruses (MSD)	Analysis of antibodies binding to coronaviruses other than SARS-CoV-2

Ad26 = adenovirus type 26; ELISA = enzyme-linked immunosorbent assay; Fc = crystallizable fragment; Ig(G) = immunoglobulin (G); MSD = Meso Scale Discovery; N = nucleocapsid; RBD = receptor-binding domain; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay.

In areas where seroprevalence is predicted to be high, a screening serologic test for past or current infection with SARS-CoV-2 may be performed (in a local laboratory) at the discretion of the sponsor to restrict the proportion of seropositive participants in the study.

A serologic test for past or current infection with SARS-CoV-2 will be performed for all participants at Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination. Samples for the serologic tests will be sent to a central laboratory for testing.[a] Participants who test positive will be informed of the result by the study staff.

8.2. Safety Assessments

Details regarding the IDMC are provided in Section 9.8 and in Appendix 3.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Appendix 4.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and reactogenicity according to the timepoints provided in the Schedules of Activities.

The Sponsor/Sponsor committee will monitor safety in a blinded manner (see Section 6.9).

8.2.1. Physical Examinations

Height and body weight will be assessed at screening. To obtain the actual body weight, participants must be weighed lightly clothed. The height should be measured without footwear.

A targeted physical examination will be performed during a COVID-19 episode by the investigator or designated medically trained clinician (or a trained HCP or home health care nurse under supervision of the investigator, if allowed per local regulations). Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF.

8.2.2. Vital Signs

At all visits, body temperature (oral route preferred, or in accordance with the local standard of care) will be assessed.

[a] Vaccination with Ad26.COV2.S may interfere with some serologic assays utilized at local community health clinics/commercial laboratories, by seeking and identifying the spike protein in the vaccine and rendering a false positive result. For this reason, participants will be encouraged to not seek testing outside the study. If a participant requires testing outside of the protocol-mandated testing schedule, the site will guide them on the appropriate assay that identifies the viral nucleocapsid protein (and not the spike protein).

Participants in the Safety Subset will utilize an e-Diary to record body temperature measurements from the time of vaccination until 7 days after each vaccination in the eCOA (see Section 8).

All participants with COVID-19 signs and symptoms should measure body temperature daily (oral route preferred, or in accordance with the local standard of care) and record the highest temperature in the last 24 hours each day in the ePRO in the eCOA, for the duration of follow-up of COVID-19 episodes (as defined in Section 8.1.2).

Vital signs will be measured during a COVID-19 episode by a qualified member of the study site. This includes measurement of, preferably, supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature. It is recommended that vital signs are measured before collection of nasal swabs and blood draws.

Blood pressure and pulse/heart rate measurements will be assessed in a supine position (preferably) with a completely automated device. Manual techniques will only be used if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be performed before blood draws and preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Under special circumstances such as high altitude, the investigator should assess baseline respiratory rate and other vital signs, as appropriate.

Any vital signs measurements taken at home that may trigger the severe/critical case definition will be confirmed as soon as possible by qualified medical staff and participants will be referred for care, if needed.

8.2.3. Pregnancy Testing

A urine pregnancy test for participants of childbearing potential will be performed at screening and before each vaccination.

Additional serum or urine pregnancy tests may be performed for participants of childbearing potential, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.3. Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, MAAEs, and product quality complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver or surrogate) during the reporting periods detailed below.

Further details on AEs, SAEs, MAAEs, and PQCs can be found in Appendix 4.

8.3.1. Time Period and Frequency for Collecting Adverse Event, Medically-attended Adverse Event, and Serious Adverse Event Information

All Adverse Events

For all participants:

- (S)AEs that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.
- Clinically relevant medical events not meeting the above criteria and occurring between signing of the ICF and moment of 1st vaccination will be collected on the Medical History eCRF page as pre-existing conditions.
- All SAEs and all AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of 1st vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.
- MAAEs are defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered medically-attended visits. New onset of chronic diseases will be collected as part of the MAAEs. MAAEs are to be reported for all participants from the moment of 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
- Special reporting situations, whether serious or non-serious, will be recorded for each vaccination from the time of vaccination until 28 days post-vaccination.
- All AEs will be followed until resolution or until clinically stable.

For participants in the Safety Subset:

- Solicited AEs, collected through an e-Diary, will be recorded for each vaccination from the time of vaccination until 7 days post-vaccination. If these solicited signs and symptoms are not resolved by that time, the participant will continue to complete the e-Diary until Day 29 post-vaccination or until they are resolved, whichever comes first.
- All other unsolicited AEs, whether serious or non-serious, will be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

Serious Adverse Events

All SAEs, as well as PQCs, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

SAEs, including those spontaneously reported to the investigator before the end of the study, must be reported using an SAE form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Participants will be reminded once a month to contact the study site in case of an SAE.

All study participants will be monitored for SAEs for up to 2 years after their last vaccination.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at injection site) and systemic events for which the participant is specifically questioned, and which are noted by participants in their e-Diary.

The first 1,000 participants will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 1,000 participants no acute reactions have been observed, the observation period at the study site may be reduced to at least 15 minutes after each vaccination for the remaining participants in the study.

In addition, after each vaccination, participants in the Safety Subset will record solicited signs and symptoms in an e-Diary from time of vaccination until 7 days post-vaccination. If these solicited signs and symptoms are not resolved by that time, the participant will continue to complete the e-Diary until Day 29 post-vaccination or until they are resolved, whichever comes first. Participants in the Safety Subset will be provided with an e-Diary and instructions on how to complete the diary (see Overview in Section 8). Electronic diary information will be transferred from the e-Diary source to the sponsor. After review and verbal discussion of the initial e-Diary entries with the participant, the investigator will complete his/her own assessment in the relevant sections of the eCRF/eCOA. Once a solicited sign or symptom from an e-Diary is considered to be of severity Grade 1 or above, it will be recorded as a solicited AE.

Solicited Injection Site (Local) Adverse Events

Participants will be asked to note in the e-Diary occurrences of injection site pain/tenderness, erythema, and swelling at the study vaccine injection site daily for 7 days after each vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in the references.[30,39]

Solicited Systemic Adverse Events

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the e-Diary in the evening of the day of each vaccination, and then daily for the next 7 days approximately at the same time each day. If more than 1 measurement is made on any given day, the highest temperature of that day will be recorded in the e-Diary.

Fever is defined as endogenous elevation of body temperature ≥38.0°C or ≥100.4°F, as recorded in at least 1 measurement.[43]

Participants will also be instructed on how to note signs and symptoms in the e-Diary on a daily basis for 7 days after each vaccination (day of vaccination and the subsequent 7 days), for the following events: fatigue, headache, nausea, myalgia.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

Medically-attended Adverse Events

MAAEs are AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. New onset of chronic diseases will be collected as part of the MAAEs. Routine study visits will not be considered medically-attended visits.

8.3.3. Follow-up of Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, MAAE, SAE, or PQC as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.

AEs, including pregnancy, will be followed by the investigator as specified in Appendix 4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the

protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from study vaccinations but will remain in the study and will continue to undergo all procedures for surveillance and follow-up of COVID-19 and all safety follow-up as outlined in the protocol for all participants.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

(S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

8.4. Virology Assessments

Nasal swabs will be used to detect and/or quantify SARS-CoV-2. Exploratory quantification of the SARS-CoV-2 viral load in saliva samples will also be performed.

Gene sequencing may be performed to detect changes in the S gene and potentially also other parts of the viral genome, if a sample is available.

Nasal swabs collected during a confirmed COVID-19 episode may also be tested at a central laboratory for the presence of other respiratory pathogens using a broad respiratory pathogens panel.

All confirmed COVID-19 episodes will be communicated to the respective participant and to other authorities according to local regulations.

Participants, with stable/well-controlled HIV infection, will be encouraged to have HIV RNA viral load and CD4 cell count assessed at least twice a year and to provide these data for inclusion in the eCRF.

8.5. Medical Resource Utilization

Medical resource utilization data over the last 3 months, associated with medical encounters, will be collected by interview with the participant and recorded in the eCRF by the investigator and study-site personnel at baseline (for all participants, concerning MRU within the last 3 months before 1st vaccination), and on COVID-19 Day 3-5 and COVID-19 Day 29 (for all participants during a COVID-19 episode; which is defined to be resolved after having 2 consecutive SARS-CoV-2 negative nasal swabs and 2 consecutive days with no COVID-19-related signs or symptoms; see Section 8.1.2]) (Appendix 7). Medical resource utilization data will also be collected through the MA-COV form (Appendix 8). This form will be provided to the participant at the 1st vaccination visit and should be completed by the medical care provider or the study site personnel during medical visits for COVID-19 or COVID-19 complications. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including selected procedures (inpatient and outpatient)
- Duration and type of mechanical ventilation and ECMO use
- Duration of hospitalization (total days length of stay, including duration by wards; eg, ICU)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

8.6. Risk Factor Assessment

If allowed by local regulations and if the participant consents, he/she will be interviewed on characteristics related to his/her current work situation, living situation, and community interactions (See Appendix 12) prior to vaccination on Day 1 and at other timepoints, on changes compared to Day 1. These characteristics can potentially be useful to identify the risk of individual participants in acquiring COVID-19 and will be used in several analyses including correlate analysis.

Risk factor data initially collected at screening from the participants, prior to implementation of the protocol amendment 2 will also be used for the planned risk-factor analysis.

8.7. Participant Medical Information Prior to, During and After the Study (Real-world Data)

In the US, for consenting participants, medical data from 5 years prior to study enrollment until 5 years after study completion, such as electronic health records, claims and laboratory data from other care settings, may be accessed utilizing tokenization and matching procedures. These data together with data collected as part of the study as specified in the Schedules of Activities, may be used to conduct exploratory analyses to enhance our understanding of the impact of prior medical history on the response to immunization and the impact of immunization on efficacy and duration of efficacy as well as adverse events that may occur during and after completion of the study (see

Section 9.5.4). The utilization of tokenization and matching procedures allows for the medical data to be obtained without violation of participant confidentiality (Sections 4.2 and 4.2.1). The real-world medical data, which are not collected as part of the study, will not be part of the clinical study database.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

Refer to Section 3 for the statistical hypotheses.

The study will have 3 timepoints for analysis:

1. The primary efficacy analyses to evaluate the primary and secondary objectives of this study (Sections 9.5.1 and 9.5.2) will be performed as soon as the TNE has been reached, or earlier based on sequential monitoring (details in Section 9.5.1). Sponsor unblinding will occur but investigator and participants remain blinded until study completion (end-of-study analysis). After the primary analysis, additional analyses to support health authority interactions may be planned, if deemed appropriate

2. The final analysis will be performed when the last participant completes the visit 12 months after the last vaccination or discontinues earlier.

3. The end-of-study analysis will be performed when all participants have completed the visit 24 months after the last vaccination or discontinued earlier

9.2. Sample Size Determination

9.2.1. Efficacy (Total Sample Size)

The study TNE is determined using the following assumptions:

- a VE for molecularly confirmed, moderate to severe/critical SARS-CoV-2 infection of 65%.
- approximately 90% power to reject a null hypothesis of H0: VE≤30%.
- type 1 error rate $\alpha = 2.5\%$ to evaluate VE of the vaccine regimen (employing the sequential probability ratio test [SPRT] to perform a fully sequential design analysis; detailed in Section 9.5.1).
- a randomization ratio of 1:1 for active versus placebo

Events are defined as first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition in Section 8.1.3.1 in the PP population at least 14 days after the 2nd vaccination with study vaccine (Day 71).

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 104, based on events in the active vaccination and placebo group, according to the primary endpoint case definition of moderate to severe/critical COVID-19 (Section 8.1.3.1).

If the primary hypothesis testing is successful, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%. The method to perform hypothesis testing of primary and secondary objectives preserving the FWER will be specified in the SAP. The FWER will be controlled at 2.5%.

Sample Size Justification

Based on the variations in seroprevalence, degree of social distancing and use of personal protective equipment, it is not feasible to estimate the incidence rates that can be attained at the time of the start of this study. It is also unknown which local regulations (eg, potential lockdowns) will be in effect at that time.

The sample size is approximately 15,000/group (30,000 in total) and is determined based on estimated annualized incidence rate of moderate to severe/critical COVID-19 of 1% to 4% at the start of the study.

Assuming 2 months of recruitment and 10% seroprevalence, the selected sample size will have a high probability (approximately 90%) to have reached an efficacy signal within 15 months after first participant vaccinated for an assumed VE≥65% under an assumed incidence of 1.4% in Month 1-3, and waning of incidence thereafter, eg, 50% reduction at Month 4 (0.70% annualized) followed by further reduction to 0.58%.

Due to the sequential monitoring, an efficacy signal can be concluded as soon as the prespecified boundary is crossed.

With higher incidences at the start of the study, the timelines to efficacy will shorten.

The operating characteristics of the study design, statistical methods, study monitoring rules and efficacy evaluations specified in this protocol with the chosen event and sample sizes will be described in a separate modeling and simulation report and will be added to the SAP before the first participant is vaccinated.

9.2.2. Immunogenicity Subset

All participants included in the Immunogenicity Subset (N=400) will be added randomly during Stage 2 of the study. Healthy adults and elderly will be assigned to subset 1a and 1b respectively, while adults and elderly with comorbidities will be assigned to subset 2a and 2b respectively, with approximately 100 participants per group as displayed in Table 2.

A sample size of 400 participants, distributed as described in Table 2, is estimated to be sufficient to allow robust description of immune responses to Ad26.COV2.S vaccine. These numbers are expected to provide a solid understanding of the magnitude and kinetics of the humoral response induced by the Ad26.COV2.S vaccine.

9.2.3. Immunogenicity Correlates (Correlates Subset)

Correlates will be assessed in a subset where immune responses and transcriptome modifications are measured in all vaccine recipients who experience a SARS-CoV-2 event, and in random samples of vaccine recipients who have not been infected, in a 1:5 ratio. The goal of this case–control study is to assess correlates of risk of SARS-CoV-2 infection (and potential other secondary endpoints) in the vaccine group by comparing vaccine-induced immune responses and transcriptome modifications associated with COVID-19. Also, placebo participants will be included in this subset (placebo infected, seropositive [based on N-protein] non-infected and seronegative non-infected), if feasible.

Correlates will also be investigated via a case-cohort design, including measurement of immunological markers in a random subcohort augmented by infected and symptomatic cases.

Placebo controls will be matched with cases from the same stage (comorbidities), age, and other co-factors as deemed appropriate. These will be detailed in the Correlates SAP.

9.2.4. Safety (Safety Subset)

While mild to moderate reactogenicity (local injection site and systemic reactions) are expected, AEs that preclude further vaccine administration (if applicable) are not anticipated.

Unsolicited AEs will be captured for a period of 28 days after each vaccination. Solicited and unsolicited AEs will be captured in the Safety Subset, ie, approximately 6,000 participants (~3,000 from the active group, ~3,000 from the placebo group; and including at least 2,000 from the older age group [≥60 years of age] if feasible).

SAEs will be captured in all participants and throughout the entire study. MAAEs (including new onset of chronic diseases) will be captured in all participants until 6 months after the last vaccination, except for MAAEs leading to study discontinuation, which are to be reported during the entire study. Based on a sample size of approximately 30,000 participants, and approximately 15,000 in the active vaccination group, for SAEs, the observation of 0 events in the database would be associated with 95% confidence that the true rate is less than 0.01%. Table 4 shows the probabilities of observing at least 1 event (solicited, unsolicited, or SAE) in 1 of the groups at given true AE rates.

Table 4: Probability of Observing at Least 1 Adverse Event or Serious Adverse Event at a Given True Adverse Event Rate in the Active Group (With a Total Sample Size of 30,000 Participants)

True AE Rate	Probability of Observing at Least 1 Adverse Event in the Active Group in N Participants	
	Solicited/Unsolicited AEs N=3,000	SAEs N=15,000
0.01%	26%	78%
0.1%	95%	100%
≥0.5%	100%	100%

AE = adverse event; N = number of participants receiving study vaccine (Ad26.COV2.S or placebo); SAE = serious adverse events

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Full Analysis Set (FAS): All randomized participants with at least 1 documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment. Analyses of safety will be performed on the FAS. Vaccine efficacy analyses can be repeated using the FAS.

Safety Subset: subset of the FAS for the analysis of solicited and unsolicited AEs.

Per-protocol Efficacy (PP) population[a]: Participants in the FAS who receive 2 doses of study vaccine and who are seronegative at the time of 1st vaccination and at Day 71, and who have no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine. The PA of VE will be based on the PP population. The PP will be the main analysis population for efficacy analyses.

Per-protocol Immunogenicity (PPI) population[a]: All randomized participants who receive 2 doses of study vaccine, including those who are part of the Immunogenicity Subset and for whom immunogenicity data are available, excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, for participants who experience a SARS-CoV-2 event (molecularly confirmed), samples taken after the event and samples taken outside protocol windows will not be taken into account in the assessment of the immunogenicity. The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants who are part of the Immunogenicity Subset for whom immunogenicity measures are available. Excluded samples might be taken into account as well in the sensitivity analysis. Analyses of vaccine immunogenicity and immune correlates of risk will be based on PPI.

The list of major protocol deviations to be excluded from the efficacy and/or immunogenicity analyses will be specified in the SAP and/or this list will be reported into protocol deviation dataset of the clinical database before database lock and unblinding.

9.4. Participant Information

For all participants, descriptive statistics of demographic (eg, gender, age, height, weight, BMI, race, and other baseline characteristics) will be provided by vaccination group. Additional characteristics related to current work situation, living situation, and community interactions will be collected for risk factor analysis, if allowed per local regulations. Risk factor data initially collected at screening from the participants, prior to implementation of the protocol amendment 2 will also be used for the planned risk-factor analysis. See also Section 9.5.3.

[a] If a participant would be vaccinated out of window due to a study pause, this will not by default be a reason for excluding this participant from the PP and PPI population. A sensitivity analysis might also be performed. Further details will be described in the SAP.

9.5. Efficacy Analyses

The SAP will be finalized prior to first participant in and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.5.1. Primary Endpoint Evaluation

The study is designed to test the primary hypothesis of VE in the PP population: H0: VE ≤30% versus H1: VE >30% and will be evaluated at a 2.5% one-sided significance level.

The primary endpoint will evaluate the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition in Section 8.1.3.1, with onset at least 14 days after the 2nd vaccination (Day 71) with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

Participants included in the seronegative analysis set are those participants with a negative SARS-CoV-2 serology test result at baseline.

Considering the current COVID-19 pandemic, early detection of VE will be very important. The proposed current analysis setup is designed for continuous sequential analyses (see Section 9.5.1.1), where statistical hypothesis testing is conducted repeatedly on accumulating data, generating an earliest possible signal if and when the splits between the number of events in placebo recipients are much larger compared to the Ad26.COV2.S-vaccinated group in such a way that they are unlikely to be due to chance alone using a truncated SPRT.

A successful primary efficacy conclusion will require establishing the hypothesis H1: VE>30% for the primary endpoint.

To evaluate the primary null hypothesis: H0: VE ≤30% versus H1: VE >30% for the primary endpoint, the truncated sequential probability ratio test will be used based on accumulating event data. This boundary is set up using the fully sequential design and is derived in such a way to have approximately 90% power to detect a VE=65% using a one-sided alpha=0.025 against H0:VE≤30%. The specific boundaries will be detailed in the SAP.

The monitoring can start as soon as the following conditions are met:

1. A minimum of 6 COVID-19 cases for the ≥60 years age group
2. At least 20 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19

No interim evaluation will be done, until those conditions are fulfilled. Monitoring for efficacy will not start before the above conditions 1-2 and will occur at least once a week by the SSG of the IDMC until the prespecified boundaries have been crossed.

The minimum criteria that may trigger the primary analysis are listed below and the SAP will describe the additional criteria in detail:

1. a) An interim evaluation if both prespecified efficacy boundaries have been met OR if 104 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 are observed

   AND

   b) The above 2 conditions are met.

OR, alternatively,

2. If the prespecified non-efficacy has been met (evaluating events with start 14 days after the second vaccination) or when the harm boundary has been crossed. The decision rules for harm and non-efficacy are detailed in Section 9.5.1.1.

If more than 104 primary endpoints are observed before the 2 conditions above are met, a single analysis will take place as soon as the conditions are met, using the full 2.5% one-sided significance level.

If the prespecified boundary and above conditions are met, the SSG will inform the IDMC and, if deemed appropriate by the IDMC, a meeting with the IDMC and the Sponsor Committee will be set up to discuss the efficacy signal. Upon this meeting the Sponsor Committee can trigger internal decision procedures to initiate health authority interactions based on the outcome of the study. If deemed appropriate based on the data, the Sponsor Committee will send the reviewed data package to a designated unblinded team independent of the study team (including a clinician, a statistician, a statistical programmer, and a regulatory person) through a secured medium, who will ensure the complete package meets the requirements for a regulatory interaction and is subsequently transmitted securely to the appropriate regulatory agency (refer to Sections 9.5.1.1 and 9.8 for more details). However, the study sites and participants will remain blinded to allow for evaluation of durability of VE. The study team will remain blinded until the database for primary analysis is locked.

If, in the event of waning incidence, it is clear that the necessary number of events cannot be collected with the available sample size within a reasonable timeframe, the PA may still be conducted based on the available data and prespecified decision rules. An operational rule that warrants for waning incidence will be specified in the SAP.

The primary efficacy analysis will pool data across populations (with and without comorbidities) to evaluate the primary and secondary objectives. In addition, these will be supplemented with a subgroup analysis for age and comorbidities employing a descriptive summary including 95% confidence intervals to describe the VE in each subpopulation.

In addition, to assess potential time-effects of VE, the Kaplan-Meier method will be used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate cumulative VE over time, defined as [(1 minus ratio (vaccine/placebo) of cumulative incidence by time t) ×100%].

Furthermore, VE will be evaluated in seronegative participants, counting primary endpoints since onset after the first vaccination.

Of note, the data may pooled with data of other ongoing efficacy studies in support of health authorities interactions.

9.5.1.1. Study Monitoring

Table 5: Specification of Sequential Statistical Analyses

Parameter	Population	Hypothesis	Statistical Method	Criterion	Monitoring Plan
Potential Harm[a] of Symptomatic Cases	FAS	H_0: VE ≥0% vs. H_1: VE <0%	Exact 1-sided binomial test of the fraction of infections assigned to who receive the vaccine.	Constant p-value cut-off controlling α at 5%	After every event starting from the 12th event [b]
Potential Harm[a] of Severe Cases	FAS	H_0: VE ≥0% vs. H_1: VE <0%	Exact 1-sided binomial test of the fraction of infections assigned to who receive the vaccine.	Unadjusted p-value α at 5%	After every event starting from the 5th event
Non-efficacy	PP	H_0: VE ≥40% vs. H_1: VE <40%	Exact 95% CI	Upper limit of the 95%CI <40%	Every 2 weeks, starting from the 20th event after 14 days post-dose 2 (Day 71)[b]
Efficacy	PP	H_0: VE ≤30% vs. H_1: VE >30%	Sequential probability ratio test	Controlling the family-wise error rate α at 2.5%	Starting from the 20th event[c] 14 days post-dose 2 (Day 71), **then at least once a week**

CI = confidence interval; FAS = full analysis set; PP = per-protocol; VE = vaccine efficacy.
[a] Harm in the form of an increased rate of symptomatic COVID-19 events due to vaccination (which meet the mild, moderate or severe/critical case definition).
[b] Monitoring stops when the primary efficacy analysis is triggered.
[c] The monitoring can only start as soon as the conditions outlined in Section 9.5.1 are met.

All boundaries will be monitored by an SSG. Once a boundary has been crossed, the SSG will inform the IDMC and an IDMC meeting will be organized. The statistical details of the decision rules and the frequency of evaluation and operational implementation will be fully detailed in the SAP and IDMC Charter.

Sequential Probability Ratio Test

Following the notation of Dragalin et al. (2002) and Dragalin and Fedorov (2006),[24,25] consider, X_1 and X_2 the number of events in respectively the placebo group and the vaccine group. The distribution of X_1 and X_2 can be approximated by a Poisson distribution with the following parameters: $\lambda_i = n_i p_i$ $(with\ i = 1,2)$. Thus, the conditional distribution of X_2 given $T = X_1 + X_2 = \mathrm{t}$ approximately follows a binomial distribution with parameters (t, π), where $\pi = \frac{\lambda_2}{(\lambda_1+\lambda_2)} = \frac{n_2 p_2}{n_1 p_1 + n_2 p_2} = \frac{1-VE}{2-VE}$, with VE=1-RR, $RR = \frac{p_2}{p_1}$, assuming a vaccine group allocation ratio of 1:1. Consequently, testing the null hypothesis $H0: VE = VE_0$ against $H1: VE = VE^*$ is equivalent to testing $H0: \pi = \pi_0$ against $H1: \pi = \pi^*$ the conditional binomial test.

Consider $\alpha = P(reject\ H0 | VE = VE0)$ and $\beta = P(accept\ H0 | VE = VE^*)$. Rejecting H0 occurs when $X_2 <= C_\alpha$ with C_α=$C_\alpha(T)$ calculated to preserve α over all the sequential looks such that

$P(X_2 <= C_\alpha|\pi = \pi_0) = B(C_\alpha; T, \pi_0) \leq \alpha$. With $B(.;T,\pi)$ the cumulative binomial distribution function with parameter T and π. The solution to the above equation, T^*, is the smallest T such that $B(B^{-1}(\alpha; T, \pi_0); T, \pi^*) \geq 1 - \beta$, with $B^{-1}(\alpha; T; \pi)$ the α-quantile of the cumulative binomial distribution function with parameters T and π.
The implemented critical boundaries for success are based on the truncated SPRT for which success boundaries are set based on observing X_2 events on the vertical axis out of total T events on the horizontal axis.

9.5.2. Secondary Endpoints

All secondary endpoint analyses will occur in the PP analysis set, in seronegative participants unless otherwise indicated.

To evaluate the effect of the vaccine against symptomatic molecularly confirmed COVID-19, including mild infections, a BOD endpoint will be evaluated based on the first occurrence of molecularly confirmed COVID-19, including mild, moderate and severe/critical case definitions in Sections 8.1.3.1 and 8.1.3.2, with onset at least 14 days after the 2nd vaccination (Day 71) with Ad26.COV2.S versus placebo, in the PP population, including all events across age groups, with and without comorbidities. In this study, the BOD endpoint is defined as taking the value 1 for mild and moderate disease and the value 2 for severe disease (implicitly assigning a value of 0 for no disease [not infected or asymptomatic infection]). By assigning higher weight to severe infections, the BOD endpoint aims at providing higher statistical power for differentiating from placebo vaccines with increased protection against severe infections (but potentially lower vaccine efficacy against milder infections). The BOD evaluates the severity-adjusted VE against preventing symptomatic incidence. The hypothesis to evaluate the vaccine efficacy against symptomatic infection will be based on this method. In addition, the VE against each severity category according to the case definition (severe, moderate, mild) will be summarized separately. Statistical significance for the BOD endpoint will be tested using H0:VE≤0 at a one-sided α=2.5% according to multiplicity adjusted strategy. Details on the calculation of VE for the BOD endpoint and its associated confidence interval (for testing) and hypothesis testing will be foreseen in the SAP.

At the time of the primary analysis VE against any infection will be evaluated. At the time of the primary analysis, available N-ELISA measurements will be incorporated to evaluate VE against any infection, including asymptomatic infection. A participant will be defined as having any infection whether he/she had either a symptomatic infection (mild, moderate or severe according to the case definition) or an asymptomatic infection (as defined in Section 8.1.3.4). When all participants had 6 months of follow-up, the available N-ELISA measurements will be used to evaluate VE against asymptomatic/undetected infections only. Poisson regression will be used to estimate the VE and associated 95% confidence interval in seronegative participants in the PP analysis set for each of both analyses.

Among participants with SARS-CoV-2 infection, the effect of the study vaccine on the viral load levels at and after diagnosis as well as on the duration of SARS-CoV-2 viral load positivity will be evaluated.

The effect of the vaccine will be evaluated against molecularly confirmed COVID-19 infections requiring medical intervention once sufficient events are available. Medical interventions are evaluated as a composite endpoint of hospitalization, ICU admission, mechanical ventilation and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings. Poisson regression will be used to estimate the VE and the associated 95% confidence interval in seronegative participants in the PP analysis set.

All VE evaluations will be repeated regardless of their serostatus.

The statistical analysis for secondary endpoints, multiple testing strategy to evaluate the secondary objectives and the timing of the hypothesis testing will be detailed in the SAP.

See also Section 9.5.1.

9.5.3. Exploratory Endpoints

Exploratory endpoint analyses will be detailed in the SAP.

If appropriate, subgroup or covariate-adjusted analyses may be performed. These subgroups/covariates may include baseline demographics and other characteristics.

9.5.4. Other Analyses

Participant Medical Information Prior to, During and After the Study (Real-world Data, in US Participants Only)

The exploratory analyses that may be conducted using the real-world data will be detailed in a SAP and results may, partially, be reported separately from the VAC31518 Clinical Study Report(s).

Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by intervention group.

9.6. Immunogenicity Analyses

No formal statistical testing of the immunogenicity data is planned. All immunogenicity analyses will be performed on the PPI set. Key tables might be repeated for the FAS (including samples that are excluded from the PPI analysis).

9.6.1. Immunogenicity Subset

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (eg, geometric mean and 95% confidence interval for the neutralization assay and ELISA) will be calculated for continuous immunologic parameters at all timepoints. Geometric mean fold rises from baseline and corresponding 95% confidence intervals might additionally be calculated. Baseline is considered as the last available assessment before vaccination. Graphical representations of immunologic parameters will be made as applicable.

The impact of baseline factors on the humoral responses will be explored graphically or via descriptive statistics. In addition, in a subset of 400 participants (the Immunogenicity Subset; ~200 from the active group, ~200 from the placebo group), humoral immunogenicity samples are taken on more occasions.

9.6.2. Correlates of Risk

If VE is demonstrated, correlates of risk will be explored. Details with appropriate methods will then be provided in a separate analysis plan.

9.7. Safety Analysis

No formal statistical testing of safety data is planned. Safety data according to the vaccination received and based on the FAS will be analyzed descriptively. The analysis of solicited and unsolicited AEs will be restricted to a subset of the FAS (ie, the Safety Subset).

For SAEs and MAAEs the full FAS is considered. New onset of chronic diseases will be collected as part of the MAAEs.

Subanalyses (descriptive) will be performed on participants with stable/well-controlled HIV infection to evaluate the effect of the vaccine on HIV RNA viral load and CD4 cell count.

Adverse Events (Solicited and Unsolicited)

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All Reported AEs with onset during the active vaccination phase (ie, AEs occurring after vaccination up to 28 days after each vaccination), and all SAEs/MAAEs will be included in the analysis. (S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study vaccine group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue the study due to an AE or who experience a severe or a serious AE.

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The number and percentages of participants with at least 1 solicited local (at injection site) or systemic AE will be presented. Solicited AEs shown in the tables and listings will be based on the overall assessment of the investigator. The overall frequencies by vaccine group as well as frequencies according to severity and duration will be described for solicited AEs. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term, while those of solicited AEs will be presented only by preferred term.

Vital Signs

For all participants, weight and height (and BMI) at baseline will be summarized using descriptive statistics. Temperature will be measured at each scheduled timepoint and summarized using

descriptive statistics. Other vital signs may be measured at the discretion of the investigator. Vital signs abnormalities will be listed.

For COVID-19 cases, temperature will be summarized over time from start of symptoms, using descriptive statistics and/or graphically. For systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and pulse oximetry, values and the percentage of participants with values beyond clinically relevant limits will be summarized at each scheduled timepoint. Descriptive statistics will be calculated for changes between COVID-19 Day 29 and COVID-19 Day 3-5.

Physical Examinations

For all participants, physical examinations can be performed at the discretion of the investigator. Physical examination abnormal findings will be listed.

For COVID-19 cases, physical examination findings and the percentage of participants with values beyond clinically relevant limits will be summarized at each scheduled timepoint. Descriptive statistics will be calculated for changes between COVID-19 Day 29 and COVID-19 Day 3-5, if available.

9.8. Interim Analysis and Committees

The study will be formally monitored by an IDMC. In general, the IDMC will monitor safety data on a regular basis to ensure the continuing safety of the participants. Enrollment will not be paused during these safety reviews, except after Stage 1 (approximately 1,000 participants). The IDMC will review unblinded data. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

Continuous monitoring for vaccine-associated enhanced disease will be performed through the SSG who will look at each of the diagnosed FAS COVID-19 events. Vaccine harm monitoring will be performed for severe/critical COVID-19/death endpoint based on the FAS. As these events will be monitored in real-time, and, after each confirmed respective case, the SSG will assess if a stopping boundary is reached. Specifically, monitoring for a higher rate of severe/critical disease or death in the vaccine group compared to the placebo group starts at the 5th event and at each additional event until the harm boundary is reached or until the primary analysis is triggered. If the stopping boundary is met, then the SSG immediately informs the Chair of the IDMC through secure communication procedures. At this point the IDMC will convene and provide a recommendation to the Sponsor Committee. As such, the potential harm monitoring is in real-time, resulting in the earliest indication of harm possible as soon as data come in. In addition, the IDMC will formally monitor the SARS-CoV-2 events to conclude both non-efficacy and efficacy (for more details on the evaluation of and monitoring for efficacy, see Section 9.5.1 and 9.5.1.1, respectively). The IDMC will evaluate in an unblinded fashion whether superiority is established for the primary endpoint or whether non-efficacy is shown based on a report provided by the SSG, when the prespecified boundaries have been crossed.

The study will also be monitored for operational non-efficacy to evaluate whether enough events to perform the PA can be collected within reasonable time. For that purpose, a monitoring rule will be set up to assess the probability that the minimal needed target number of primary endpoint events to be able to perform the PA in the PP set will be reached. Two versions of the non-efficacy monitoring report will be generated. A report provided to the IDMC will contain unblinded events and a report provided to the Sponsor Committee will contain blinded events. While it is the primary responsibility of the Sponsor Committee to make decisions regarding study operations and modifications based on monitoring of study vaccine-blinded primary events from the study, the IDMC can evaluate the progress towards primary endpoint targets in the context of the study vaccine-unblinded data, and based on this review may recommend to the Sponsor Committee to complete the study early due to reaching a boundary for efficacy or non-efficacy to assess VE (see Section 9.5.1).

The monitoring rules will be detailed in the IDMC charter, with the statistical details in the SAP.

The SAP will describe the planned analyses in greater detail.

9.9. Analyses for cohort unblinded due to administration of an authorized/licensed COVID-19 vaccine

Investigators may receive requests to unblind study participants who become eligible to receive an authorized/licensed COVID-19 vaccine if/when these become available. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorized/licensed vaccine according to local immunization guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures. The reason for the unblinding request should be documented.

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. In the event the participant is unblinded, no further study vaccination will be permitted. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the Schedules of Activities to the extent that they permit. Safety, efficacy and immunogenicity evaluations will be identical for all participants, if applicable and feasible, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, including participants in the safety subset, if applicable and feasible. All data will be analyzed separately from the point of unblinding for safety, efficacy and immunogenicity, as described in the Statistical Analysis Plan.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	adenovirus type 26
AdVac®	adenoviral vaccine
AE	adverse event
ART	anti-retroviral treatment
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
BOD	burden of disease
CDC	Centers for Disease Control and Prevention
CEC	clinical evaluation committee
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CT	computed tomographic
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
eDC	electronic data capture
ePRO	electronic patient-reported outcomes
ELISA	enzyme-linked immunosorbent assay
ERD	enhanced respiratory disease
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FC	crystallizable fragment
FDA	Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
FOIA	Freedom of Information Act
FWER	family-wise error rate
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCP	health care professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IM	intramuscular(ly)
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IWRS	interactive web response system
MAAE	medically-attended adverse event
MA-COV	medically-attended COVID-19
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus

MIS	multisystem inflammatory syndrome
MRU	medical resource utilization
N	nucleocapsid
NHP	non-human primate
PA	primary analysis
PaO_2	partial pressure of oxygen
PP	Per-protocol (efficacy)
PPI	Per-protocol Immunogenicity
PQC	product quality complaint
RBD	receptor-binding domain
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse-transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	severe acute respiratory syndrome
SARS-CoV(-2)	severe acute respiratory syndrome coronavirus(-2)
SIC	Symptoms of Infection with Coronavirus-19
SIPPM	site investigational product and procedures manual
SpO_2	oxygen saturation
SPRT	sequential probability ratio test
SSG	statistical support group
SUSAR	suspected unexpected serious adverse reaction
Th(1/2)	T-helper cell (type 1/2)
TNE	target number of events
TNF-α	tumor necrosis factor alpha
US	United States
VE	vaccine efficacy
VNA	virus neutralization assay
vp	virus particles
WHO	World Health Organization

Definitions of Terms

COVID-19	COVID-19 is the disease caused by the virus SARS-CoV-2. COVID-19 refers to SARS-CoV-2 infection with symptoms, and can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death.[57,58]
eCOA	An umbrella term encompassing different types of outcomes assessments, in particular, the COVID-19 signs and symptoms surveillance question, the ePRO and the e-Diary.
ePRO	The electronic technology used to collect the patient-reported outcome data. PROs are reports that come directly from the participant without interpretation by clinician or anyone else. This includes the SIC questionnaire (Symptoms of Infection with Coronavirus-19) and the recording of pulse oximetry results.
e-Diary	The electronic technology used to record solicited signs and symptoms by the participants in the Safety Subset.
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedules of Activities:

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	Timepoints
Testing done locally	• Urine pregnancy testing for participants of childbearing potential only	• At screening and before each vaccination • At additional timepoints as determined necessary by the investigator or required by local regulation
	• Serum pregnancy testing for participants of childbearing potential only	• At timepoints as determined necessary by the investigator or required by local regulation
	• Nasal swabs for virology testing (molecular confirmation of SARS-CoV-2 infection using a test approved by FDA-EUA or equivalent)	• On COVID-19 Day 1-2 (nasal swab collected by the participant at home) • On COVID-19 Day 3-5 (nasal swab collected by qualified study staff) • Once every 2 days following COVID-19 Day 3-5, until closure of the COVID-19 procedures (nasal sample collected by the participant at home)
	• Serology blood sample for sero-confirmation of SARS-CoV-2 infection using a test approved by FDA-EUA or equivalent	• At screening (at the discretion of the sponsor)
Testing done centrally *Note: samples for molecular confirmation of SARS-CoV-2 infection will be tested centrally if the participant met the prespecified criteria for suspected COVID-19 on COVID-19 Day 1-2 or Day 3-5, as determined locally.*	• Nasal swab for virology testing (molecular confirmation of SARS-CoV-2 infection and viral load testing)	• At baseline (nasal swab collected by qualified study staff) • On COVID-19 Day 1-2 (nasal swab collected by the participant at home) • On COVID-19 Day 3-5 (nasal swab collected by qualified study staff) • Once every 2 days following COVID-19 Day 3-5, until closure of the COVID-19 procedures (nasal swab collected by the participant at home)
	• Saliva samples for virology testing (molecular confirmation of SARS-CoV-2 infection and viral load testing)	• On COVID-19 Day 3-5 (saliva sample collected by the participant at the study site or at home) • Once every 2 days following COVID-19 Day 3-5, until closure of the COVID-19 procedures (saliva sample collected by the participant at home)

Laboratory Assessments	Parameters	Timepoints
	• Serum samples for humoral immunogenicity	• Non-Immunogenicity Subset: on study visits 2, 5, 7, 8, and the early exit visit (if applicable) • Immunogenicity Subset: on study visits 2, 3, 4, 5, 7, 8, 9, 10, and the early exit visit (if applicable)
	• Serum sample for sero-confirmation of past SARS-CoV-2 infection	• On Day 1 (before the 1st vaccination) and 14 days, 6 months, and 1 year after the 2nd vaccination • COVID-19 Day 29
	• Serum sample for humoral immunogenicity	• On COVID-19 Day 3-5 and COVID-19 Day 29
	• Nasal swab for virology testing (other respiratory pathogens using a broad respiratory pathogens panel)	• May be performed on samples collected during a confirmed COVID-19 episode and in a subset of samples from participants with a symptomatic infection.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study vaccine to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Consent of each participant must be obtained according to local requirements after the nature of the study has been fully explained. The informed consent(s) must be obtained before performance of any study-related procedure. Downloading of an application to the participant's eDevice, to access materials for enrollment and study information, is not considered a study-related procedure. The ICF can be signed remotely prior to the Screening Visit.

The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the

participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

As described in Section 8.1.2, a caregiver may assist a participant who is unable to complete the SIC in the eCOA, by reading the questions aloud and recording the responses in the eCOA on the participant's behalf (using the caregiver's unique identifier and PIN). For this purpose, a caregiver consent form has been developed. Consent must be obtained according to local requirements and must be obtained from the caregiver before he or she is allowed to complete the eCOA on behalf of the participant. After having obtained the caregiver's consent, a copy of the consent form must be given to the caregiver. Of note, the caregiver is not intended to be a Legally Authorized Representative who can provide informed consent for study participation on behalf of the participant. It is also not the intent that the caregiver collects nasal swabs or other samples from the participant unless he or she is specifically qualified to perform these tasks and can document the use of appropriate personal protective equipment during the performance of such tasks.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.COV2.S, to understand SARS-CoV-2 infection, to understand differential vaccine responders, and to develop tests/assays related to Ad26.COV2.S and SARS-CoV-2 infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1).

10.3.6. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. Enrollment will not be paused during these safety reviews, except after Stage 1 (approximately 1,000 participants). This committee will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

Ad hoc review may be performed further to the occurrence of any SAE leading to a study pausing situation as outlined in Section 6.9, or at request of the sponsor's medical monitor or designee. The principal investigator and sponsor's study responsible physician will inform the IDMC of any AE of concern.

If the SSG assesses that the stopping boundary is met (see below), the Chair of the IDMC will immediately be informed through secure communication procedures. At this point, the IDMC will convene and provide a recommendation to the Sponsor Committee.

In addition, the IDMC will formally monitor the infections in all groups to conclude both non-efficacy and efficacy. The IDMC will evaluate in an unblinded fashion whether superiority is established for the primary endpoint or whether non-efficacy is shown (see Section 9.8) based on a report provided by the SSG, when the prespecified boundaries have been crossed. The boundaries are based on the SPRT.

The sponsor designated teams and/or Sponsor Committee reviews all clinical and laboratory safety data during the course of the study.

Statistical Support Group

The SSG is the statistical support group to the IDMC; they are unblinded and provide the with the statistical analysis based on unblinded data. As the IDMC, they are independent to the company. They will continuously monitor for vaccine-associated enhanced disease by looking at each diagnosed COVID-19 case in the FAS (and also SARS-CoV-2 infections in participants requiring hospitalization; and SARS-CoV-2 infections in participants being admitted to the ICU [or equivalent]; and SARS-CoV-2 infections resulting in death [with death being at least probably related to COVID-19]). As these infections will be monitored in real-time, and, after each confirmed respective case, the SSG will assess if a stopping boundary is reached. If the stopping boundary is met, then the SSG immediately informs the Chair of the IDMC through secure communication procedures. At this point the IDMC will convene and provide a recommendation to the Sponsor Committee. As such, the potential harm monitoring is in real-time, resulting in the earliest indication of harm possible as soon as data come in.

Clinical Evaluation Committee

A CEC will be established to evaluate the diagnosis, severity, and duration of each COVID-19 identified case in the study. This committee is not an endpoint adjudication committee but will independently evaluate the severity of the COVID-19 cases. A comparison between the official case definition endpoint and CEC evaluation will be made. The CEC will consist of independent clinical infectious disease experts and a pulmonologist. Clinical evaluation committee deliberations per case and conclusions will be documented by the CEC and will be provided to the Sponsor. The CEC are blinded to study vaccine assignment.

Sponsor Committee

It is the primary responsibility of the Sponsor Committee to make decisions regarding study operations and modifications based on monitoring of study vaccine-blinded primary events from the study.

If any pausing rule is met (Refer to Section 6.9) and if following appropriate safety review, it is deemed appropriate to restart dosing, the Sponsor must submit a request to restart dosing with pertinent data to competent authority as a request for a substantial amendment, as required by local regulations or authority request (e.g MHRA). If needed, this will be followed by a substantial amendment of the IB and/or protocol.

The Sponsor Committee responsibilities, authorities, procedures and their interactions with the IDMC will be documented in the IDMC Charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding Ad26.COV2.S or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information

in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad26.COV2.S, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per-protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end-of-study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review the eCRF for accuracy and completeness after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study will be recorded in the eCRF or eCOA. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).

- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility (including relevant medical history, including anything related to footnotes i and j to the Schedules of Activities), and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant therapy; study vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to ePRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Participant- and investigator-completed scales and assessments designated by the sponsor (ie, SIC) will be recorded directly into an eDevice and will be considered source data. The participant's e-Diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data. The documentation of the positive RT-PCR result that serves as a trigger to start procedures for COVID-19 follow-up, will be considered source data.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary, if allowed per local regulations. If on-site monitoring visits are not possible due to local regulations, restrictions and guidance, the monitor will conduct site monitoring visits and activities remotely. Additional on-site monitoring visits may be needed at a later moment in time to catch up on source data review.

Remote source data review of electronic records might be performed if possible and if allowed by local/national regulations, restrictions and guidance.

The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will review the source documents (eg, hospital/clinic/physician's office medical records) to ensure adherence to the protocol. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for review by the sponsor study-site contact. If electronic records are maintained at the study site, the method of review must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of source document review and may be needed to ensure that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. Remote auditing techniques may also be utilized, if necessary. These audits will require access to all study records, including (electronic) source documents as allowed per local regulations, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study

documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study vaccine development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

For the Safety Subset, any respiratory tract infection will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. Any respiratory tract infection recorded as an AE in the eCRF will be excluded from the AE analysis if the molecular test is subsequently found to be positive for SARS-CoV-2. Respiratory tract infections arising from SARS-CoV-2 infection will not be reported as (S)AEs in the Clinical Study Report but will be tabulated separately.

Note: For time period of sponsor's AE collection, see All Adverse Events under Section 8.3.1.

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgement should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately

life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event (eg, death from anaphylaxis), the event must be reported as a SUSAR even if it is a component of the study endpoint (eg, all-cause mortality).

Any respiratory tract infection fulfilling the criteria of an SAE will be reported as such during the entire study. If the molecular test is positive for SARS-CoV-2, the SAE will be excluded from the SAE analysis in the Clinical Study Report and will be tabulated separately.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.COV2.S, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study vaccine is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study vaccine administration and the AE.

Not Related

There is not a reasonable causal relationship between study vaccine administration and the AE.

The term “reasonable causal relationship” means there is evidence to support a causal relationship.

By definition, all solicited AEs at the injection site (local) will be considered related to the study vaccine administration.

10.4.3. Severity Criteria

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on version of September 2007[54], included in Appendix 9.

For AEs not identified in the grading table, the following guidelines will be applied:

Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities and requires medical intervention
Grade 4	Potentially life-threatening	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability OR ER visit or hospitalization

For participants in the Safety Subset, the severity of solicited signs and symptoms will be graded in the e-Diary by the participant based on the severity assessment provided in the diary as well as assessed by the investigator using the toxicity grading scale in Appendix 9. (*Note*: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever]). See also Section 8.3.2.

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study vaccine in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Known overdose of a sponsor study vaccine
- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Safety Report Form of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible,

diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). *Note*: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be

considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study vaccine, is considered a SAE.

Information regarding SAEs will be transmitted to the sponsor using a SAE Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5.

Definition of a Person of Childbearing Potential

A Person of Childbearing Potential

A person is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

A Person Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is 1 in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal person experiences menarche) or the risk of pregnancy changes (eg, a person who is not heterosexually active becomes active), a person must begin an acceptable effective method of contraception, as described throughout the inclusion criteria.

10.6. Appendix 6: Symptoms of Infection with Coronavirus-19 (SIC)

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

10.7. Appendix 7: MRU Questionnaire

Baseline Version

Participant ID: _____

Date (dd-mmm-yyyy): _____

1. Medical consultations

In the last 3 months, how many times have you had medical consultations?

	No	Yes	Type of contact (personal consultation /telemedicine)	If yes, specify the number of visits	Indicate a reason for each visit
General Practitioner/Nurse practitioner					
Internal Medicine/Medical Outpatient Department					
Other Specialist (Please specify):					
Other (eg Physiotherapy, Pharmacist for a consultation Please specify):					

2. Professional home care

Please indicate the need for professional care at home in the last 3 months.

	No	Yes	Type of contact (personal consultation /telemedicine)	If yes, specify the number of visits	Indicate a reason for each type of professional care
General Practitioner					
Nurse/ Nurse practitioner					
Internal Medicine/Medical Outpatient Department					
Other Specialist (Please specify):					
Other (eg Physiotherapy, Pharmacist Please specify:)					
Supplemental oxygen					

3. Hospital Services

In the last 3 months, did you visit the hospital?

Yes: ____

No: ____

	No	Yes	If yes, specify the number of visits/admissions	If yes, specify the length of each stay/use (days)	Indicate a reason for each hospital visit
Emergency Department*					
Short-term hospital visit (<24 hours admission)					
Hospitalization in general ward[#]					
Hospitalization in intensive/critical care					
Mechanical ventilation use					

*Please count Emergency Department visits only if the visit did not result in a hospital admission.

[#]Please capture type of ward and length of stay in each ward.

4. Institutional care admission(s) other than hospital

Yes: ____

No: ____

Please indicate if there has been any need for admission for care in a long-term facility, in the last 3 months.

	No	Yes	If yes, specify number of admissions	If yes, specify the length of stay (days)	Indicate a reason for each institutional care admission
Long-term facilities					
Rehabilitation facility					
Supplemental oxygen					

Version for Confirmed COVID-19 Cases

Participant ID: _____

Date (dd-mmm-yyyy): _____

1. Medical consultations

Since onset of the confirmed COVID-19 episode, how many times have you had medical consultations?

	No	Yes	Type of contact (personal consultation/ telemedicine)	If yes, specify the number of visits	Specify number of visits related to COVID-19 or its complications	Indicate a reason for each visit
General Practitioner						
Internal Medicine/Medical Outpatient Department						
Other Specialist (Please specify):						
Other (eg Physiotherapy, Pharmacist for a consultation Please specify:)						

2. Professional home care

Please indicate the need for professional care at home since onset of the confirmed COVID-19 episode

	No	Yes	Type of contact (personal consultation/ telemedicine)	If yes, specify the number of visits	Specify number of visits related to COVID-19 or its complications	Indicate a reason for each type of professional care at home
General Practitioner						
Nurse/ Nurse practitioner						
Internal Medicine/Medical Outpatient Department						
Other Specialist (Please specify):						
Other (eg Physiotherapy, Pharmacist Please specify:)						
Supplemental oxygen						

3. Hospital Services

Since onset of the confirmed COVID-19 episode, did you visit the hospital?

Yes: ____

No: ____

	No	Yes	If yes, specify number of visits/admissions	Specify number of visits/admissions related to COVID-19 or its complications	Specify the length of each stay/use (days)	Indicate a reason for each hospital visit
Emergency Department*						
Short-term hospital visit (<24 hours admission)						
Hospitalization in general ward[#]						
Hospitalization in intensive/critical care						
Mechanical ventilation use						

*Please count Emergency Department visits only if the visit did not result in a hospital admission.

[#]Please capture type of ward and length of stay in each ward.

4. Institutional care admission(s) other than hospital

Please indicate if there has been any need for admission for care in a long-term facility, since onset of the confirmed COVID-19 episode.

Yes: ____

No: ____

	No	Yes	If yes, specify number of admissions	Specify number of admissions related to COVID-19 or its complications	Specify the length of each stay (days)	Indicate a reason for each institutional care admission
Long-term facilities						
Rehabilitation facility						
Supplemental oxygen						

10.8. Appendix 8: Medically-attended COVID-19 (MA-COV) Form

Section 1: To be completed in all healthcare settings[a] (eg, family doctor, nurse practitioner, outpatient clinic, emergency department visits, and hospitalizations).

Participant ID (to be completed by study staff):
Date of visit:
Name and role of healthcare professional completing form:
Contact details for healthcare professional:

DIAGNOSIS/DIAGNOSES
Please list diagnosis/ diagnoses made during the patient's clinical interactions at this facility.

MEDICATIONS
Please list any new medications prescribed or changes in medication dosing.

CLINICAL NARRATIVE INCLUDING COURSE OF INFECTION

COVID-19 DIAGNOSTIC TEST

Was a COVID-19 diagnostic test performed? □ **Yes** □ **No**
If 'yes' selected, please fill out remaining questions below

Specify diagnostic method: _____

Specify test name and manufacturer: _____

Date performed: _____

Type of sample taken:_

□ **Nasal swab sample** □ **Saliva sample**

□ **Sputum sample** □ **Other (specify):** _____

Specify results: _____

VITAL SIGNS
Has vital sign assessment been performed?

[a] The MA-COV form should be completed by the medical care provider or study site personnel during medical visits for COVID-19 or COVID-19 complications.

□ **Yes** □ **No**

Temperature (°C/°F): _____

Respiratory rate: _____

Pulse: _____

Systolic and Diastolic Blood Pressure: _____

Oxygen saturation: _____

- **Does the subject have a clinically abnormal oxygen saturation?**
  □ **Yes** □ **No**
- **If yes, is the oxygen saturation adjusted for altitude per the investigator judgement:**
  □ **≤93%** □ **>93%**

DIAGNOSTIC TESTING

Was a peak flow measurement made? □ **Yes** □ **No**

If yes, please indicate date performed: _____ _____

Peak flow (L/min): _____

Was a chest X-ray and/or CT performed? □ **Yes** □ **No**

If yes, please indicate date performed: ___

What percentage of the lung was involved? _____

Was an arterial blood gas measured? □ **Yes** □ **No**

If yes, please indicate date performed: _____

Specify results:
pH: _____; pCO_2 (mmHg): _____; pO_2 (mmHg): _____; HCO_3 (mEq/L): _____; O_2 saturation (%):_____

Were additional diagnostic tests performed? □ **Yes** □ **No**

If yes, please specify diagnostic method:

Date performed: _____

Specify results: _____

SIGNS AND SYMPTOMS

In case the severity and/or start and/or end date of any of the experienced signs and symptoms are known, please indicate.

Did the patient experience any of these events, signs or symptoms?

- **Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute or heart rate ≥125 beats/minute or SpO_2 ≤93% on room air at sea level[a], or PaO_2/FiO_2 <300 mmHg)**
  □ **Yes** □ **No**

[a] SpO_2 criteria will be adjusted according to altitude per investigator judgement.

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Respiratory failure requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Respiratory rate ≥20 but <30 breaths/minute**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Shortness of breath**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Heart rate ≥90 beats/minute**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Shock (systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm Hg or requiring vasopressors)**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Radiologic evidence of DVT**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Significant acute renal or hepatic dysfunction**

□ **Yes** □ **No**

Severity: □ **Mild** □ **Moderate** □ **Severe**

□ **Start date:** _____ □ **End date:** _____

- **Hyperinflammatory Syndrome**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Symptoms or signs of stroke**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Numbness, tingling, or weakness face or limbs**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Difficulty speaking or forming speech**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Difficulty understanding speech**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Feelings of confusion**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Clinical or radiological evidence of pneumonia**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Fever (≥38.0°C or ≥100.4°F)**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Shaking chills or rigors**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Cough**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Sore throat**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Malaise**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Headache**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Myalgia**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Gastrointestinal symptoms**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Chilblains/pernio (red or bruised looking feet or toes)**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

- **Anosmia (olfactory or taste disorders)**

  □ **Yes** □ **No**

  Severity: □ **Mild** □ **Moderate** □ **Severe**

  □ **Start date:** _____ □ **End date:** _____

MANAGEMENT	
ANY TYPE OF MANAGEMENT OTHER THAN MEDICATION?	□ **Yes** □ **No**

If yes, please specify:

- **Nebulizer treatments**
  - □ **Yes** □ **No**
- **IV fluids**
  - □ **Yes** □ **No**
- **Intubation**
  - □ **Yes** □ **No**

Section 2: COVID-19-related Procedures completed during the event.

SUPPLEMENTAL OXYGEN	
Was supplemental oxygen administered?	□ **Yes** □ **No**

If 'yes' selected, please fill out remaining questions in this section.

Type of supplemental oxygen administration:

□ **Invasive Mechanical Ventilation**
□ **Non-Invasive Mechanical Ventilation**
□ **Nasal Cannula**
□ **Nonrebreathing Face Mask with Reservoir and One-Way Valve**
□ **Venturi Mask**
□ **Simple Face Mask**
□ **Reservoir Cannulas**

□ **Other: _____**

If invasive mechanical ventilation, specify:

□ **Through endotracheal tube** □ **Through tracheostomy tube**

If non-invasive mechanical ventilation, specify:

□ **Continuous positive airway pressure** □ **Bilevel positive airway pressure**

Oxygen concentration and units: _____

Start date and time: _____

End date and time (if applicable): _____

Has supplemental oxygen administration returned to that level provided prior to the current respiratory illness?
□ **Yes** □ **No**

DIALYSIS	
Was dialysis performed?	□ **Yes** □ **No**

If yes, please specify:

ANY OTHER PROCEDURES PERFORMED	
Were any other procedures performed?	□ **Yes** □ **No**

If yes, please specify the procedure and reason:

- **Procedure:_____**
- **Reason performed: _____**

10.9. Appendix 9: Toxicity Grading Scale

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007)

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain/Tenderness[#]	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement	Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever	Hospitalization; Pain/tenderness causing inability to perform basic self-care function
Erythema[#]	25 – 50 mm	51 – 100 mm	>100 mm	Hospitalization; Necrosis or exfoliative dermatitis
Swelling[#]	25 – 50 mm	51 – 100 mm	>100 mm	Hospitalization; Necrosis

[#] Revised by the sponsor.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	>40 >104.0
Tachycardia - beats per minute	101 – 115	116 – 130	>130	Hospitalization for arrhythmia[#]
Bradycardia - beats per minute***	50 – 54	45 – 49	<45	Hospitalization for arrhythmia[#]
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	<80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

* Participant should be at rest for all vital sign measurements.

** For oral temperature: no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

[#] Revised by the sponsor.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting[#]	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization; Hypotensive shock
Nausea[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities	Hospitalization; Inability to perform basic self-care functions
Diarrhea[#]	2 – 3 loose stools or <400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or >800 gms/24 hours or oral rehydration necessary	Hospitalization; Hypotensive shock OR IV fluid replacement indicated
Headache[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Fatigue[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Myalgia[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions

[#] Revised by the sponsor.

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

10.10. Appendix 10: Symptoms of Coronavirus (US Centers for Disease Control and Prevention)

The following extract shows symptoms of coronavirus infection as listed on the US CDC website (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) dated 13 May 2020.

Watch for symptoms

People with COVID-19 have had a wide range of symptoms reported – ranging from mild symptoms to severe illness. Symptoms may appear **2-14 days after exposure to the virus.** People with these symptoms may have COVID-19:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

This list does not include all possible symptoms. CDC will continue to update this list as we learn more about COVID-19.

10.11. Appendix 11: Summary of Guidance from CDC Website on Underlying Medical Conditions That Lead or Might Lead to Increased Risk for Severe Illness From COVID-19

People of any age with **certain underlying medical conditions** are at increased risk for severe illness from COVID-19:

People of any age with the following conditions **are at increased risk** of severe illness from COVID-19:

- Cancer
- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Immunocompromised state (weakened immune system) from solid organ transplant
- Obesity (body mass index [BMI] of 30 or higher)
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease
- Type 2 diabetes mellitus

COVID-19 is a new disease. Currently there are limited data and information about the impact of underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we know at this time, people with the following **conditions might be at an increased risk** for severe illness from COVID-19:

- Asthma (moderate to severe)
- Cerebrovascular disease (affects blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension or high blood pressure
- Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
- Neurologic conditions, such as dementia
- Liver disease
- Pregnancy
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Smoking
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2 Fcoronavirus% 2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. Accessed: 19 July 2020.

10.12. Appendix 12: Risk Factor Assessment

10.12.1. Questionnaire 1

Are you a student? ☐ Yes ☐ No
If Yes – Are you likely to return to school in person in 2020? ☐ Yes ☐ No ☐ I don't know
Are you retired? ☐ Yes ☐ No

How often do you go in person to your main workplace (other than work-from-home)?
☐ 0 days/week ☐ 1 day/week ☐ 2-4 days/week ☐ 5 or more days/week

Does your main workplace have social distancing measures in place?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable
Is your main workplace cleaned on a regular basis?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable
Do people in your main workplace use personal protection equipment (such as masks)?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable
How do you get to work? (Check all that apply)
☐ Drive own car ☐ Carpool ☐ Rideshare (Taxi, Uber, Lyft, others)
☐ Bus ☐ Train / Subway ☐ Walk / Bike
☐ Frequent Air Travel ☐ Not applicable
On a typical day, how many people do you interact with in person at work?
☐ No one ☐ Between 1 and 10 people
☐ Between 11 and 30 people ☐ Between 31 and 50 people
☐ More than 50 people
On a typical day, how many people do you interact with in person outside of work?
☐ No one ☐ Between 1 and 10 people
☐ Between 11 and 30 people ☐ Between 31 and 50 people
☐ More than 50 people

Living Situation
Do you live in any of the following (choose all that apply):
☐ Single family home ☐ Multi-family housing (apartment building, condo)
☐ Long-term care facility ☐ Assisted-living facility
☐ Dormitory ☐ RV / Trailer
☐ Single room in a hotel ☐ Shelter
☐ Other adult group setting ☐ Staying with friends / Couch surfing
☐ No residence ☐ Tribal Lands / Reservation
☐ Other
How many people do you live with (other than yourself)?
Total people under 18 years of age
Total people between 18-64 years of age
Total people over 65 years of age
Are any of the people you live with expected to return to school in person in 2020?
☐ Yes ☐ No ☐ I don't know

Community Interactions
In the last 2 weeks, have you attended any gatherings with more than 10 people? (e.g., church, party, concert, wedding, funeral, demonstration or other event). ☐ Yes ☐ No ☐ Not applicable / Don't want to tell
If yes, approximately how many people were at the largest gathering?
☐ less than 10 ☐ 10-20 ☐ 21-50 ☐ 51-250 ☐ More than 250
Was this gathering an indoor or outdoor event?
☐ Indoor ☐ Outdoor ☐ Both
How frequently do you have visitors in your residence including people completing work inside?
☐ Daily
☐ Weekly
☐ Monthly
☐ Rarely
☐ Never
☐ N/A

Over the past month, have you been in close contact with anyone that tested positive for COVID-19?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable / Don't want to tell
If yes, is this person someone that you live with?
☐ Yes ☐ No ☐ Not applicable / Don't want to tell

10.12.2. Questionnaire 2

How often do you go in person to a workplace or school (other than work or study-from-home)?	☐ 0 days/week ☐ 1 day/week ☐ 2-4 days/week ☐ 5 or more days/week
In the last week, approximately how many people were at the largest gathering you have attended (e.g., church, party, sporting, concert, wedding, funeral, demonstration or other event)?	☐ N/A ☐ 1-10 ☐ 11-20 ☐ 21-50 ☐ 51-250 ☐ More than 250
In the last week, have you been in close contact with anyone that tested positive for COVID-19? • If yes, please indicate:	☐ Yes ☐ No ☐ I don't know ____ Total number of household members that tested positive ____ Total number of non-household members that tested positive

Note: these questions may still be adapted.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 2 (27 November 2020)

Overall Rationale for the Amendment: The amendment is written to clarify that all participants that have a reverse-transcriptase polymerase chain reaction (RT-PCR) positive finding for SARS-CoV-2 from any source, even if asymptomatic, will be followed until there are two consecutive negative PCRs. In addition, text in relation to biomarker evaluation of RNAseq analyses (PAXgene tube) is deleted, and based on Health Authority request, text in exclusion criterion #7 was corrected and text regarding United Kingdom (UK) specific self-swabbing test was deleted. Finally, text was added to introduce the utilization of tokenization and matching procedures, for United States (US) participants only, to obtain participant's medical data 5 years prior to enrollment of the participant until 5 years after study completion from consenting participants.

The changes made to the clinical protocol of study VAC31518COV3009 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.2 Participants With (Suspected) COVID-19 4.1 Overall Design 8 Study Assessments and Procedures and associated subsections 10.3.10 Source Documents	Clarified that all participants that have a RT-PCR positive finding for SARS-CoV-2 from outside the study, even if asymptomatic, will be followed until there are two consecutive negative PCRs.	To ensure safety of staff and other persons coming in contact with the infected participant.
1.1 Synopsis 1.3.1 All Participants 1.3.2 Participants With (Suspected) COVID-19 3 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.3 Measures to Minimize Bias: Randomization and Blinding 8 Study Assessments and Procedures and associated subsections 9.5.4 Other Analyses 10.2 Appendix 2: Clinical Laboratory Tests 10.3.4 Data Protection	Text in relation to the evaluation of biomarker RNAseq analyses (PAXgene tube) is deleted and subsequently, the total amount of blood drawn from the participants has been adjusted.	Deletion. Collection of biomarker data from participants in Study VAC31518COV3001 is deemed sufficient, hereby the assessment was taken out from this study.
1.1 Synopsis 2.1 Study Rationale 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design	It has been clarified that Stage 2 will enroll participants with and without comorbidities and immunogenicity subset will be enrolled in Stage 2 only.	Clarification

Section number and Name	Description of Change	Brief Rationale
8.1.4 Immunogenicity Assessments 9.2.2 Immunogenicity Subset		
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination	The specification of '(>10 days)' when referring to the chronic use of systemic corticosteroids has been removed from the exclusion criterion 3 and aligned throughout.	To remove ambiguity as within the same exclusion criterion 3 b substantial immunosuppressive steroid dose is defined as ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent
6.9 Study Vaccination Pausing Rules for Stage 1 10.3.6 Committees Structure	Text was added to clarify that if there will be any study pause, the Sponsor will submit a request to restart the study with pertinent data to the Health Authorities as a request for a substantial amendment, as required by the local regulations.	Upon Health Authority feedback
1.3.1 All Participants 1.3.2 Participants With (Suspected) COVID-19 8.1.2 Procedures in the Event of (Suspected) COVID 19 8.5 Medical Resource Utilization 10.8 Appendix 8: Medically-attended COVID-19 (MA-COV) Form	The MA-COV form has been updated to also capture additional individual signs and symptoms, including clinical or radiological evidence of pneumonia, hyperinflammatory syndrome, and if the oxygen saturation for a participant is considered clinically abnormal but >93% (corrected for altitude). In addition, some clarifications were added to the form and it is clarified that the form may also be completed by the study site personnel.	To ensure collection of all necessary information in order to determine the severity of COVID-19 per the case definitions and clarification purposes.
1.1 Synopsis 5.1 Inclusion Criteria 5.2 Exclusion Criteria	Gestational diabetes has been removed from the list of comorbidities (or risk factors) that might be associated with increased risk of progression to severe COVID-19.	Gestational diabetes is not applicable in the current study VAC31518COV3009 as pregnant women are not allowed to participate in the study.
1.1 Synopsis 1.3.1 All Participants 1.3.2 Participants With (Suspected) COVID-19 4.1 Overall Design 8.1.2 Procedures in the Event of (Suspected) COVID 19 8.6 Risk Factor Assessment 9.4 Participant Information 10.12 Appendix 12: Risk Factor Assessment	It is clarified that, besides being interviewed on characteristics related to current work situation, living situation, and community interactions, as specified in Appendix 12, prior to vaccination on Day 1, they will be asked about any changes related to these characteristics at Day 71 post-vaccination 1 followed by 6 months and 1 year post-vaccination 2, and at COVID-19 Day 3-5. In addition, it was also clarified that the risk factor data initially collected at screening from the participants, before the implementation of this amendment will also be used for the planned risk factor analysis.	Clarification on when participants will be interviewed on additional characteristics that will be used for risk factor analysis.

Section number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Chronic kidney disease has been removed and participant on hemodialysis has been added to the examples of clinical conditions expected to have an impact on the immune response of the study vaccine.	There is evidence that hemodialysis has a negative impact on the immune response elicited by the vaccination.
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	Exclusion criterion 7 and text for Prestudy therapy was updated to remove remdesivir and to clarify that the use of investigational Immunoglobulin (Ig), investigational monoclonal antibodies or convalescent serum are not allowed during the study.	Upon Health Authority feedback and alignment across Ad26.COV2.S study protocols
2.3.1 Risks Related to Study Participation 10.4.4 Special Reporting Situations	It is stated more clearly that breastfeeding women are allowed to participate in the study. In alignment with this, exposure to a sponsor study vaccine from breastfeeding has been removed from the list of special reporting situations.	Breastfeeding is allowed in the current study VAC31518COV3009.
1.1 Synopsis 1.3.1 All Participants 3 Objectives and Endpoints 4.1 Overall Design 8 Study Assessments and Procedures 8.1.3 Efficacy Assessments and related subsections 10.2 Clinical Laboratory Tests	Text was deleted related to UK-specific self-swabbing test as these will not be performed.	Upon National Institute for Health Research (NIHR), UK feedback
1.1 Synopsis 5.2 Exclusion Criteria	Clarification has been added that the history of Parkinson's disease, seizures, ischemic strokes, intercranial hemorrhage encephalopathy, meningoencephalitis is exclusionary from Stage 1.	Clarification.
5.2 Exclusion Criteria	It is clarified that participants with Guillain-Barré syndrome (Exclusion criterion 16) and participants requiring hospitalization as indicated in exclusion criterion 17 are excluded from the study altogether and not only in Stage 1 of the study.	Correction
5.1 Inclusion Criteria	Clarifications have been made to the inclusion criterion 4, indicating that Stage 1 participants can have a condition that is stable and well controlled except the ones listed in exclusion criterion 14 which are associated with increased risk of progression to severe COVID-19.	Clarification

Section number and Name	Description of Change	Brief Rationale
	In addition, medication dose for allowed stable conditions (in all stages of the study) cannot have been increased within 12 weeks prior to vaccination.	
5.4 Screen Failures	It has been clarified that participants can be rescreened once, also when they meet all in- and exclusion criteria but the 28-day screening period was exceeded.	To allow participants who were found eligible to be enrolled in the study but were not randomized within the 28-day screening window to still participate in the study.
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Study Design 9.8 Interim Analyses and Committees 10.3.6 Committees Structure	Reference to a possible sample size adjustment has been deleted and sample size considerations has been added.	Correction: per the VAC31518COV3009 Amendment 1, the sample size of approximately 30,000 participants was selected based on available epidemiology data at the time of Amendment 1 writing.
1.3.1 All Participants	It is clarified that the diagnostic molecular RT-PCR test for SARS-CoV-2 infection (from nasal swab taken at baseline) will be performed at a central laboratory on a retrospective basis. These baseline results are not available in real time, and thus cannot be used to inform participants at time of enrollment.	Clarification
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design	It is clarified that molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result **by a central laboratory** using a PCR-based or other molecular diagnostic test.	For clarification purposes and to align information included in Section 8.1.3 which states that molecular confirmation of SARS-CoV-2 infection by a central laboratory will be used for the analysis of the case definition.
10.3.10 Source Documents	It has been clarified that source documents for any relevant medical history and prestudy therapies determining eligibility (ie, as specified in the footnotes to the Schedule of Activities) of the participants needs to be collected	To ensure that all necessary information to properly assess SAEs (relatedness) is collected.
1.1 Synopsis 5.2 Exclusion Criteria	The list of comorbidities (or risk factors) that are or might be associated with an increased risk of progression to severe COVID-19 has been corrected from 'uncontrolled human immunodeficiency virus (HIV) infection' to 'HIV infection'	Correction
1.1 Synopsis 8.1.3.1 Case Definition for Moderate to Severe/Critical COVID-19	It has been clarified that the adjustment according to altitude for the SpO_2 criteria is per the investigator judgement.	Clarification

Section number and Name	Description of Change	Brief Rationale
10.8 Appendix 8: Medically-attended COVID-19 (MA-COV) Form		
8.3.6 Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	It has been clarified that (S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately.	Alignment across different sections of the protocol.
1.1 Synopsis 8.1.4 Immunogenicity Assessments	The list of immunoassays used in support of exploratory endpoints has been completed	Addition of missing assay.
1.1 Synopsis 1.3.1 All Participants 1.3.2 Participants With (Suspected) COVID-19 4.1 Overall Design 8 Study Assessments and Procedures and associated subsections	Term "COVID-19 signs and symptoms surveillance" is changed to "(Suspected) COVID-19 surveillance (symptom check)" and additional clarification is provided by adding this to the procedures followed for participants with (suspected) COVID-19.	Clarification
1.1 Synopsis 1.3.1 All Participants 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.2.1 Study-Specific Ethical Design Considerations 8.7 Participant Medical Information Prior to, During and After the Study (Real-world Data) 9.5.4 Other Analyses 10.1 Appendix 1: Abbreviations 11 REFERENCES	Addition of the utilization of tokenization and matching procedures to obtain medical data 5 years prior to enrollment of the participant until 5 years after the participant completed the study from consenting participants in the US.	Participant medical data (electronic health records, claims, laboratory data from other care settings) prior to, during and following participation in the study (real-world data) is important to obtain in order to better understand the impact of prior medical history on the response to immunization and the impact of immunization on efficacy and duration of efficacy as well as adverse events that may occur during and after completion of the study. The technique proposed to obtain this data, ie, tokenization and matching procedures, allows for such data to be obtained without violation of participant confidentiality. This collection of real-world data will only be conducted for consenting participants from the US where this technique is feasible
1.1 Synopsis 8 Study Assessments and Procedures 9.3 Populations for Analysis Sets	Clarified that when the study pause has been lifted, efforts will be made to still vaccinate a participant if the vaccination window is missed due to the study pause. Clarified that these participants will not be excluded from the per protocol efficacy (PP) and per protocol immunogenicity (PPI) population by default for this reason.	Mitigation in case of study pause: Clarification on out of window vaccination.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 All Participants 6.8 Prestudy and Concomitant Therapy 8.3.1 Time Period and Frequency for Collecting Adverse Event, Medically-attended Adverse Event, and Serious Adverse Event Information 8.3.2 Method of Detecting Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events	Clarified that if solicited signs and symptoms are not resolved within 7 days post-vaccination, the participant will continue to complete the e-Diary until Day 29 post-vaccination or until they are resolved, whichever comes first. Similarly, the concomitant therapies will also be collected by the participants and recorded in the eCRF until Day 29 post-vaccination or until they are resolved, whichever comes first.	Clarification
9.5.2 Secondary Endpoints	The text about the endpoint of molecularly confirmed COVID-19 cases requiring medical intervention has been added.	Addition: to align the secondary endpoints described with the secondary endpoints that are part of the hypothesis testing.
1.1 Synopsis 9.3 Populations for Analysis Sets	PP population has been corrected to include seronegative test at Day 71 sample.	Correction
5.2 Exclusion Criteria	Text has been added to restrict the proportion of seropositive participants in the study.	Clarification
8 Study Assessments and Procedures	Clarification has been added that visits apart from screening and vaccination can be performed at participant's home by the study staff or designee	Clarification
8 Study Assessments and Procedures	Clarification has been added that in case of home visit, assessments that cannot be delegated to a designee must be performed by an appropriate Site staff member via a phone call or telemedicine.	Clarification
1.3.2 Participants With (Suspected) COVID-19 8.1.2 Procedures in the Event of (Suspected) COVID 19	Further clarifications are made to the procedures to be followed in case of (suspected) COVID-19.	Clarification
6.9 Study Vaccination Pausing Rules for Stage 1 8.2 Safety Assessments 10.1 Appendix 1 Abbreviations 10.3.6 Committees Structure	Text has been corrected to remove the reference to collaboration partners, PI and PSRT, as there will be no collaboration partners involved and PI review is not planned. The safety data will be reviewed by Sponsor/Sponsor committee, as applicable and not PSRT.	Correction
1.1 Synopsis 1.3.1 All Participants 2.1 Study Rationale 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Study Design	Text about the equal distribution of participants in 2 age groups (≥18 to <60 years and ≥60 years of age) in Stage 1 and equal distribution of first 1000 participants has been deleted.	Based on accumulating safety data from study VAC31518COV3001, safety evaluation of approximately 1000 participants without comorbidities will trigger the enrolment of participants with and without comorbidities.

Section number and Name	Description of Change	Brief Rationale
8.3.2 Method of Detecting Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events		
7.1 Discontinuation of Study Vaccination 7.2 Participant Discontinuation/Withdrawal From the Study	Further clarification was added on the consent withdrawal by the participants.	Clarification
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design	Clarification has been added that the enrollment might be stopped if the primary endpoint will be reached.	Clarification
2.3.1 Risks Related to Study Participation 5.1 Inclusion Criteria 11 REFERENCES	It has been clarified that the use of condoms is not considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms.	Clarification
Title Page	Study Title has been changed from "HORIZON" to "ENSEMBLE 2".	To clarify that this study is strongly linked to study VAC31518COV3001, which is referred to as the ENSEMBLE study. To allow harmonization across our Ad26.COV2.S program and to assist the public with associating both studies and, assisting the public with identifying an appropriate study site, and distinguishing dosing across both studies.
Title page	Prepared by line removed.	To align with internal guidelines on legal entity to be mentioned on title page.
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Minor clarifications are made.

Amendment 1 (25 September 2020)

Overall Rationale for the Amendment: The amendment is written to adjust the dose level of Ad26.COV2.S from 1×10^{11} virus particle (vp) to 5×10^{10} vp based on data from the first-in-human (FIH) study VAC31518COV1001, including safety and immunogenicity data from Cohort 1a, safety data from Cohort 3 and immunogenicity data from the sentinel group of Cohort 3. Furthermore, throughout the protocol changes are made in response to the feedback received from health authorities, partners, and the community. Finally, minor errors and inconsistencies were corrected throughout the protocol.

The changes made to the clinical protocol of study VAC31518COV3009 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.1 Study Rationale 2.2 Background 4.1 Overall Design 4.3 Justification for Dose 4.4 End-of-study Definition 6.1 Study Vaccines Administered 8.1.4 Immunogenicity Assessments	The Ad26.COV2.S dose level has been changed from 1×10^{11} vp to 5×10^{10} vp.	Immunogenicity data from Cohort 1a and a sentinel group of Cohort 3 of study VAC31518COV1001 have become available. The data demonstrated that a single dose of Ad26.COV2.S at a dose level of 5×10^{10} vp is sufficient to induce an acceptable immune response that meets prespecified minimum criteria: (1) wild-type virus neutralization assay (wtVNA)[a] response rate (28 days post-Dose 1): lower limit of 95% confidence interval (CI) ≥65%; (2) T-helper cell type 1 (Th1)/T-helper cell type 2 (Th2) response magnitude ratio: Th1>Th2 within responder population and (3) pseudovirus (ps)VNA magnitude associated with protection in non-human primate (NHP) studies is induced by vaccination in humans: estimated population mean protection probability ≥40% and lower limit of 95% CI of estimated population mean protection probability ≥20%. This finding was supplemented

[a] psVNA was to be used for the seroconversion criterion, however, the psVNA was not sensitive enough to cover the range of human responses, hence wtVNA was used instead.

Section number and Name	Description of Change	Brief Rationale
		with several sensitivity analyses utilizing ELISA, a more sensitive psVNA, and statistical evaluation of attributed values below the level of sensitivity of the original psVNA. The safety data from Cohort 1a and Cohort 3 of the FIH study with the Ad26.COV2.S 5×10^{10} vp dose level were deemed acceptable. Since all criteria were met by the $5x10^{10}$ vp dose, the sponsor decided to use this dose for further evaluation in the Phase 3 study VAC31518COV3009.
1.1 Synopsis 9.5.1 Primary Endpoint Evaluation 9.5.1.1 Study Monitoring	The trigger for the evaluation of the primary endpoint has been modified, adding one condition related to the number of COVID-19 cases (6) meeting the primary endpoint definition of moderate to severe/critical COVID-19 in the elderly population, that needs to be met.	In order to ensure the evaluation of the primary endpoint provides sufficient information to assess the benefit/risk and potentially support an Emergency Use Authorization.
2.3.1 Risks Related to Study Participation 6.8 Prestudy and Concomitant Therapy	Guidance on the use of antipyretics during the study has been added.	To clarify that antipyretics are recommended post-vaccination for symptom relief, as needed. Prophylactic antipyretic use is not encouraged.
5.2 Exclusion Criteria 6.6 Continued Access to Study Vaccine After the End of the Study 6.8 Prestudy and Concomitant Therapy	Guidance has been added on the use of licensed COVID-19 vaccines, when one might become available, during the study.	Clarification purposes
1.1 Synopsis 1.3.1 All Participants 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design 8.3.2 Method of Detecting Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events	It has been clarified that the post-vaccination observation period at the study site will be at least 30 minutes for the first 1,000 participants (and not 2,000 participants) and may be decreased to at least 15 minutes for the remaining participants, if no acute reactions are observed.	To align with the number of participants included in Stage 1 since the decision to reduce the post-vaccination follow-up time at the site will be based on the planned Day 3 safety evaluation.
1.1 Synopsis 1.2 Schema 2.1 Study Rationale 4.1 Overall Design	In Stages 1a and 1b combined, the enrollment of participants aged ≥18 to <40 years will be limited to approximately 20% of the total study population. The aim of having a minimum of approximately 25% of recruited	The sponsor believes that Ad26.COV2.S is more likely to protect against more severe disease and progression of infection is age related with twice the level of severity in 50-year-olds compared to 20-year-

Section number and Name	Description of Change	Brief Rationale
	participants ≥60 years of age has been adjusted to 30%.	olds. The cap of approximately 20% of participants 18-40 years and the aim to enroll a minimum of approximately 30% elderly participants, will allow to enroll a more representative population at highest risk of severe disease per the protocol case definition.
9.2.1 Efficacy (Total Sample Size)	The time to signal has been modified in the sample size section.	To present time to signal corresponding to the assumed VE for powering the study (VE=65%).
1.1 Synopsis 1.3.1 All Participants 4.1 Overall Design 8.7 Baseline and Longitudinal Risk Factor Assessment 9.4 Participant Information 9.5.3 Exploratory Endpoints 10.12 Appendix 12: Risk Factor Assessment	It has been added that additional longitudinal characteristics related to current work situation, living situation, and community interactions, from participants who consent to this, will be collected for risk factor analysis, if allowed per local regulations.	To assess baseline and longitudinal characteristics that are potentially useful to identify the risk of acquiring COVID-19 which will be used for the correlates of protection analysis.
1.1 Synopsis 1.3.2 Participants With COVID-19-like Signs and Symptoms 4.1 Overall Design 8.1.1 Prespecified Criteria for Suspected COVID-19 8.1.2 Procedures in the Event of COVID 19-like Signs and Symptoms	It has been clarified that because several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events.	To ensure that vaccine-related events do not trigger the COVID-19 related follow-up procedures for mild disease, to be able to include cases of moderate disease that were not classifiable by the definition and for simplification and clarification purposes.
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design 4.3 Justification for Dose	Additional rationale for the assessment of the 2-dose regimen has been added.	Even though a single-dose regimen in study VAC31518COV1001 showed good immunogenicity, evaluation of the 2-dose regimen is still valuable as this regimen may show a higher and more durable immune response.
1.3.2 Participants With COVID-19-like Signs and Symptoms 8.1.2 Procedures in the Event of COVID 19-like Signs and Symptoms 10.2 Appendix 2: Clinical Laboratory Tests	The sample for sero-confirmation of SARS-CoV-2 infection to be collected on Day 3-5 in participants with COVID-19 like signs and symptoms has been removed	It is unlikely to detect antibodies 3-5 days post signs and symptoms or a positive PCR for SARS-COV-2 infection. Antibodies will likely be observed from 7 days post signs and symptoms onwards.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 All Participants 4.1 Overall Design	It is clarified that at the time of study entry, each participant will need to indicate to the study site, in case they would get infected with SARS-CoV-2, the identity and location of their routine medical care physician and/or facility and the identity and location of where they would obtain emergency care and hospitalization if necessary. If this information is not available, a plan for where such care could be obtained should be developed.	To ensure optimal follow up of participants with COVID-19.
10.3.3 Informed Consent Process	Information about the caregiver's consent form has been added.	For clarification purposes.
10.3.8 Data Quality Assurance 10.3.11 Monitoring	Source data verification has been replaced by review of the source data.	To clarify that source data verification will not be done on most of the data.
3 OBJECTIVES AND ENDPOINTS	An exploratory objective to assess the impact of the vaccine on other respiratory diseases has been added.	To obtain epidemiology data of other important respiratory infections that may be affected by COVID-19 circulation.
3 OBJECTIVES AND ENDPOINTS	A secondary endpoint looking at the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 with onset 14 days after the 1st vaccination has been added.	To allow for a pooled analysis on this timepoint across studies.
9.5.1 Primary Endpoint Evaluation	It has been clarified that the data from this study may be pooled with data from other ongoing efficacy studies.	To have a more robust data package in support of health authority interactions.
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol	Correction of minor errors and inconsistencies. Minor clarifications are made.

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INVESTIGATOR AGREEMENT

VAC31518 (JNJ-78436735) Clinical Protocol VAC31518COV3009 Amendment 3

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

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Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Javier. Ruiz Guiñazú. MD

Institution: PPD vention B.V.

Signature: _____ Date: 20-DEC-2020

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.