Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2101544

STUDY ENSEMBLE (COV3001)

This supplement contains the following items:

1. Original study protocol, final study protocol, summary of protocol amendments
2. Original statistical analysis plan, final statistical analysis plan, and summary of amendments

STUDY ENSEMBLE (COV3001)

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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

Protocol VAC31518COV3001; Phase 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

Status: Approved
Date: 22 July 2020
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-RIM-50860, 1.0

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

Confidentiality Statement

The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

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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

This study is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V) in collaboration with Operation Warp Speed (OWS), which also encompasses the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the COVID-19 Prevention Trials Network (COVPN).

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 28 days post-vaccination
Secondary *(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 post-vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 28 days post-vaccination
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b] in SARS-CoV-2 seronegative adults, as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit [ICU] admission, mechanical ventilation, and

Objectives	Endpoints
	extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomographic [CT] findings) or linked to any molecularly confirmed[a], COVID-19[b,c] at least 28 days post-vaccination
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
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 28 days post-vaccination
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 28 days post-vaccination
To assess the effect of Ad26.COV2.S on all molecularly confirmed symptomatic COVID-19[b,c], as compared to placebo	First occurrence of molecularly confirmed COVID-19[b,c] (any severity) at least 28 days post-vaccination
To assess the effect of Ad26.COV2.S on occurrence of asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline and 1-year post-vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship to vaccination of SAEs (during the entire study), MAAEs (until 6 months post-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 vaccination, and in terms of unsolicited AEs during 28 days post-vaccination	Occurrence, intensity, duration, and relationship to vaccination of solicited local and systemic AEs during 7 days after vaccination and of unsolicited AEs during 28 days post-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 – SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein)

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result 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)

Exploratory objectives and endpoints, including correlates of protection, are included in the body of this protocol.

Hypotheses

The study is designed to test the primary hypothesis of vaccine efficacy (VE) in the per-protocol (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 28 days after the 1st vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, 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% 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.

Case Definition for Moderate to Severe 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:

- Any 1 of the following new or worsening signs <u>AND</u> any 1 of the following new or worsening symptoms:

Signs	Symptoms
Respiratory rate ≥20 breaths/minute	Shortness of breath (difficulty breathing)
Abnormal saturation of oxygen (SpO_2) but still >93% on room air at sea level*	Fever (≥38.0°C or ≥100.4°F)
Heart rate ≥90 beats/minute	Cough
Clinical or radiologic evidence of pneumonia	Sore throat
Radiologic evidence of deep vein thrombosis (DVT)	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)

* SpO_2 criteria will be adjusted according to altitude.

OR

- Any 2 of the following new or worsening symptoms:

Fever (≥38.0°C or ≥100.4°F)
Shaking chills or rigors
Shortness of breath (difficulty breathing)
Cough
Sore throat
Malaise as evidenced by 1 or more of the following elements*: - loss of appetite - generally unwell - fatigue - physical weakness
Headache
Muscle pain (myalgia)
Gastrointestinal symptoms as evidenced by 1 or more of the following elements*: - diarrhea - vomiting - nausea - abdominal pain
Red or bruised looking feet or toes
New or changing olfactory or taste disorders

*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:

- 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.

- 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

Case Definition for Mild COVID-19

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

  AND at any time during the course of observation:

- One of the following symptoms: fever (≥38.0°C or ≥100.4°F), sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, muscle pain (myalgia), gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, or chills, without shortness of breath or dyspnea.

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

OVERALL DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 to <60 years of age and ≥60 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 study vaccine.

Participants will be randomized in parallel in a 1:1 ratio to receive intramuscular (IM) injections of Ad26.COV2.S or placebo as shown in the table below. Ad26.COV2.S will be administered at a dose level of 1×10^{11} virus particles (vp).

Table: Vaccination Schedule VAC31518COV3001

Group	N	Day 1
1	Up to 30,000	Ad26.COV2.S (1×10^{11} vp)
2	Up to 30,000	Placebo

N = number of participants; vp = virus particles.
Note: It is intended that a minimum of approximately 25% of recruited participants will be ≥60 years of age

A staggered enrollment strategy will be used:

- Stage 1a: Initially, 2,000 participants ≥18 to <60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 (including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients) will be enrolled, based on acceptable Day 29 safety and adequate immunogenicity data, including T-helper 1/T-helper 2 (Th1/Th2), from the corresponding age group (Cohort 1a) of the first-in-human (FIH) study VAC31518COV1001 (see body of this document for more details).
- Stage 1b: After a vaccination pause to allow the Data Safety Monitoring Board (DSMB, also known as an Independent Data Monitoring Committee [IDMC]) to examine 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from the ongoing Phase 1/2 studies]), if no safety concerns are identified enrollment will proceed, expanding enrollment to include ≥18- to <60-year-old participants with comorbidities that are associated with increased risk of progression to severe COVID-19.
- Stage 2a: Based on acceptable Day 29 safety and adequate immunogenicity (Th1/Th2) data from Cohort 3 of the FIH study VAC31518COV1001 (see body of this document for more details) and emerging safety data from Stage 1 of this Phase 3 study, 2,000 participants ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients).
- Stage 2b: After a vaccination pause (in the age group ≥60 years of age) to examine the 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from Stage 1 and the ongoing Phase 1/2 studies]) from Stage 2a by the DSMB, if no safety concerns are identified in this population enrollment will proceed, also including participants aged ≥60 years with comorbidities that are associated with increased risk of progression to severe COVID-19. Once initiated, Stage 2 may run in parallel with Stage 1 and will enroll a minimum of approximately 25% of the total study population.

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, type 2, or gestational); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and (pulmonary) hypertension or 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; Parkinson's disease; seizures;

[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. The study will remain consistent with any new information, as indicated by the US CDC. In this study, (former) smoking will not be considered as a comorbidity.

ischemic strokes; Intracranial hemorrhage; Guillain-Barré syndrome; encephalopathy; meningoencephalitis; and participants who live in nursing homes or long-term care facilities. For details and exceptions, refer to the exclusion criteria in this document.

If the post-Dose 1 data from study VAC31518COV1001 do not adequately support initiation of a single-dose vaccination regimen in study VAC31518COV3001, enrollment will not start until post-Dose 2 data from study VAC31518COV1001 are available. If the post-Dose 2 data from study VAC31518COV1001 demonstrate an adequately increased immune response that meets minimum criteria (based on protective levels from non-human primates [NHP], levels in infected people, and from other studies)[34,33] for initiation of a 2-dose vaccination regimen in study VAC31518COV3001, a regimen consisting of 2 doses of Ad26.COV2.S will be introduced via a protocol amendment.

The duration of individual participation, including screening, will be maximum 2 years and 1 month. 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 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. Biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity will also be studied. Medical resource utilization (MRU) following vaccination will be recorded for all participants with molecularly confirmed, symptomatic COVID-19.

Until 1 year post-vaccination or until the primary analysis takes place (whichever comes last), 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 post-vaccination or after the primary analysis takes place (whichever comes last), until the end of the long-term follow-up period, the frequency of this surveillance question through the eCOA will decrease to once every 2 weeks. For all participants that are lost to follow-up through eCOA and hospitalization has not been recorded, every effort will be made to document their status.

All participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19 on COVID-19 Day 1-2 and Day 3-5 should undertake the COVID-19 procedures (as described in body of this protocol) until 14 days after symptom onset (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last, unless 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 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's medical care provider will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

A DSMB will be commissioned for this study.

NUMBER OF PARTICIPANTS

Overall, a target of 30,000 to 60,000 adult participants (≥18- to <60-year-old and ≥60-year-old, 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, including in the ≥18- to <60-year-old population. The intent is to have a COVID-19 incidence in the study higher than 1% so that the sample size and enrollment period can be reduced. The actual sample size for the study, up to a maximum of 60,000 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. The sample size may be adjusted by the Sponsor Committee during the study, based on blinded data, to ensure sufficient power at the time of the primary analysis (PA). Details on the possible blinded sample-size reassessment will be described in the statistical analysis plan (SAP).

It is intended that a minimum of approximately 25% of recruited participants will be ≥60 years of age. If prior study results do not support initiation of Stage 2 (≥60-year-old participants), the study will be limited to Stage 1 (≥18- to <60-year-old participants) up to the targeted sample size. Under these circumstances, a protocol amendment may be created to modify the study to introduce a 2-dose regimen of Ad26.COV2.S in the participants ≥60 years of age, if the data generated by the 2-dose vaccination regimen in Cohort 3 of study VAC31518COV1001 demonstrate an immune response that meets criteria for initiating study VAC31518COV3001 in participants ≥60 years of age.

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 2×10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dosed at 1×10^{11} vp
- Placebo: 0.9% sodium chloride (NaCl) solution

For blinding purposes, all participants will receive Ad26.COV2.S or placebo at Day 1, 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 adult inflammatory 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.

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

[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.

asymptomatic infection. This assay will be performed on samples obtained at Day 1 (pre-vaccination) and at 1 year after vaccination.

IMMUNOGENICITY EVALUATIONS

Blood will be collected from all non-Immuno Subset participants for humoral immunogenicity assessments before the vaccination, 28 days after vaccination and at 1 year after vaccination

For a total of approximately 400 participants in the Immuno Subset (ie, 400 participants at sites with access to appropriate processing facilities), blood will be collected for analysis of humoral immune responses before vaccination, 28 days after vaccination, 70 days after vaccination, and 24, 52, 78, and 104 weeks after 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 Day 1-2), 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.

Table: Immunogenicity and Transcriptomic Assays

Humoral Assays	**Purpose**
Secondary Endpoints	
SARS-CoV-2 binding antibodies to S protein (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing 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
Exploratory Endpoints	
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
Antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein (ELISA)	Analysis of antibodies binding to the RBD of the SARS-CoV-2 S protein
Transcriptomic Assay	**Purpose**
Exploratory Endpoints	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in unstimulated cells or whole blood

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

A screening serologic test for past or current infection with SARS-CoV-2 may be performed in a local lab, only upon request and at the discretion of the sponsor, in areas where seroprevalence is predicted to be high, to restrict the proportion of seropositive participants in the study.

A baseline serologic test for past or current infection with SARS-CoV-2 will be performed for all participants. Samples for the baseline serologic tests will be sent to the central lab for testing.

SAFETY EVALUATIONS

Participants in the Safety Subset (defined below) will remain under observation at the study site for at least 30 minutes post-vaccination. After vaccination, all participants that are not part of the Safety Subset will remain under observation at the study site for at least 15 minutes to monitor for the development of any acute reactions.

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 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 (regardless of the causal relationship) are to be reported from the moment of 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 vaccination until 6 months after the 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 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 vaccination until 7 days post-vaccination.
- All other unsolicited AEs, whether serious or non-serious, will be recorded from the time of vaccination until 28 days post-vaccination.

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%.
- 90% power to reject a null hypothesis of H0: VE≤30%.
- α at 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 28 days after vaccination 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 protocol reflects the range of sample sizes that could be employed to attain the design assumptions above. The maximum sample size equals 30,000/group (60,000 in total) and is determined based on an estimated annualized incidence rate of 1% to 4% at the start of the study to reach the requirements for efficacy evaluation within the targeted time frame, as detailed above. The actual sample size for the study, up to a maximum of 60,000 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.

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 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 a 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:** Participants in the FAS who receive study vaccine and who are seronegative at the time of vaccination 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:** All randomized and vaccinated participants, including those who are part of the Immuno 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 Immuno 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 This analysis will take place as soon as the TNE has been reached, or earlier based on sequential monitoring.
2. The final analysis will be performed when the last participant completes the visit 12 months post-vaccination or discontinues earlier.
3. The end-of-study analysis will be performed when all participants have completed the visit 24 months post-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 28 days after vaccination with Ad26.COV2.S versus placebo, separately, 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.

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 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.

The PA will be triggered when the TNE of 104 is reached or earlier when a prespecified super-efficacy boundary or non-efficacy has been met (evaluating events with start 28 days after vaccination) or when the harm boundary has been crossed. Monitoring for efficacy will start from the 20th event onward after every

event by an independent statistical support group (SSG) of the DSMB until the prespecified boundary has been crossed.

If the prespecified boundary is met, the SSG will inform the DSMB and if deemed appropriate by the DSMB, a meeting with the DSMB 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 (both age groups with and without comorbidities) to evaluate the primary and secondary objectives. In addition, these will be supplemented with a subgroup analysis for age group (18 to 60 years, ≥60 years) and comorbidities employing a descriptive summary, including 95% confidence intervals to describe the VE in each subpopulation. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (>70 years, >80 years).

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

As a key secondary objective, the VE will be evaluated in participants regardless of their serostatus at the time of vaccination.

The multiple testing strategy 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 Committee(s)

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

The DSMB will review 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from the ongoing Phase 1/2 studies]) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b, respectively. Vaccination of participants in the respective age groups

will be paused during these safety reviews. Enrollment will not be paused during other safety reviews. The DSMB responsibilities, authorities, and procedures will be documented in the DSMB 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 COVID-19 disease/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 disease or death in the vaccine arm compared to the placebo arm starts at the 8th event and at each additional event until the harm boundary is reached or until the end of the study. If the stopping boundary is met, then the SSG immediately informs the Chair of the DSMB through secure communication procedures. At this point the DSMB 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 DSMB will formally monitor the SARS-CoV-2 events to conclude both non-efficacy and efficacy. The DSMB 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 FAS set will be reached. Two versions of the non-efficacy monitoring report will be generated. A report provided to the DSMB 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 and decide on potential blinded sample size reassessment to be able to reach the TNE, the DSMB 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.

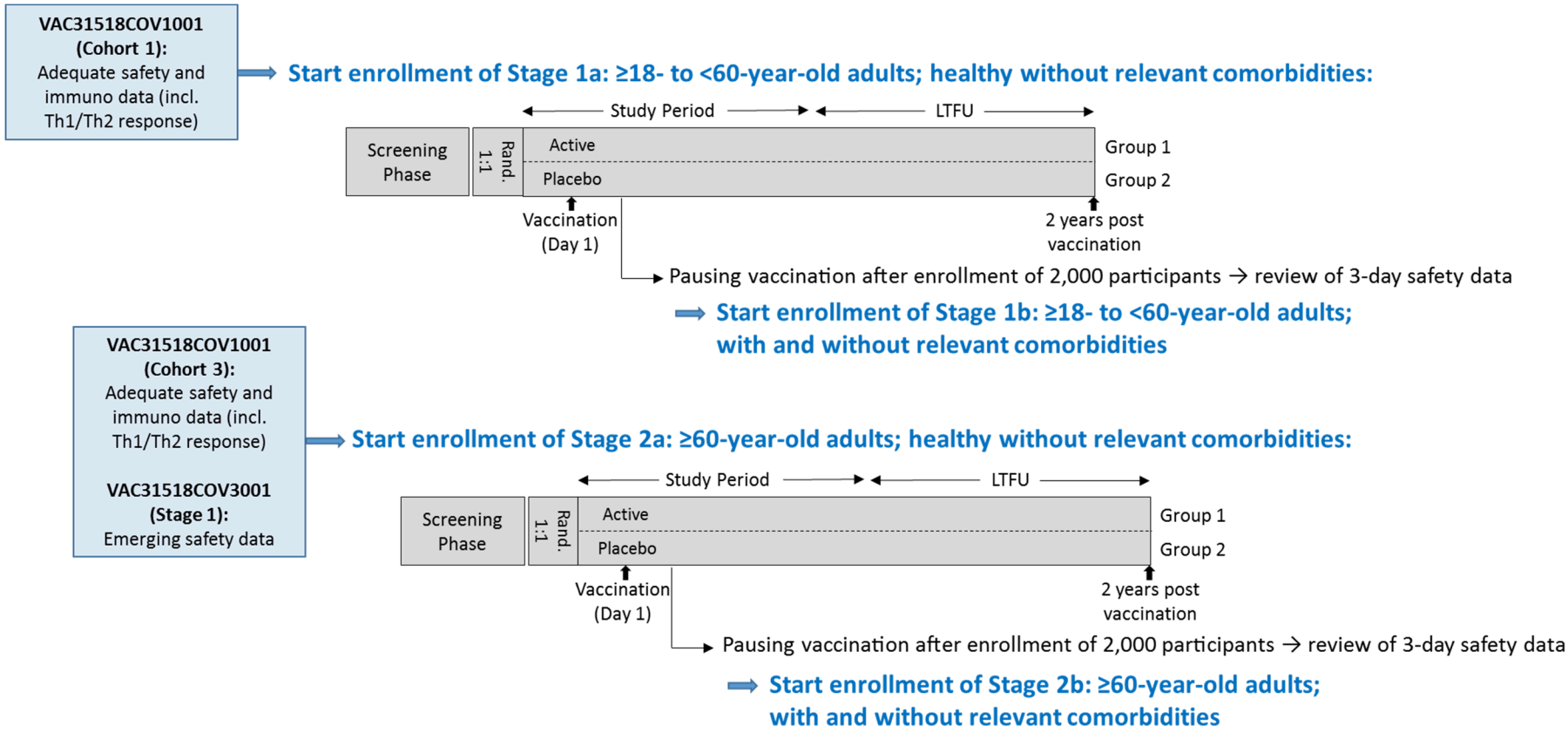
The above high-level rules are preliminary and subject to fine-tuning based on operating characteristics.

Monitoring rules will be formally finalized prior to study start and fully documented in the SAP and DSMB Charter.

The SAP will describe the planned interim analyses in greater detail.

1.2. Schema

Figure 1: Schematic Overview of the Study



Active = Ad26.COV2.S; incl. = including; LTFU = long-term follow-up; rand. = randomization; Th = T-helper cell type 1/2.
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. Once initiated, Stage 2 may run in parallel with Stage 1 and will enrol a minimum of approximately 25% of the total study population. 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 VAC31518COV3001 based on data from study VAC31518COV1001.
Refer to Section 2.2 for details about the VAC31518COV1001 study.
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[c]	5[d]	6	7	8	Exit[e]
Visit Timing		Vac	Vac + 28 d	Vac + 70 d	Vac + 24 w	Vac +52 w	Vac +78 w	Vac +104 w	
Visit Day/Week	Day -28 to 1	Day 1	Day 29	Day 71	Week 24	Week 52	Week 78	Week 104	
Visit Window			±3 d	±3 d	±21 d	±21 d	±28 d	±28 d	
Visit Type	Screening	Vaccination	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Early Exit
Informed consent[f]	●								
Inclusion/exclusion criteria	●	●[#,g]							
Demographics	●								
Relevant medical history[h]/prestudy therapies[i]	●	●[#]							
Body weight and height	●								
Vital signs[j]	●								
Body temperature[k]	●	●[#]	●	●	●[l]	●	●	●	●[m]
Urine pregnancy test[n]	●	●[#]							
Pulse oximetry		●[#]							
Randomization		●[#]							
Nasal sample collection for SARS-CoV-2 testing[o]		●[#]							
Biomarker RNAseq blood sample (PAXgene tubes, whole blood), mL[p]		●[#]2.5							
Sample collection for serological test for anti-SARS-CoV-2 antibody[q]	●								
MRU questionnaire (baseline version)[r]		●[#]							
Pre-vaccination symptoms[s]		●[#]							
eCOA training and set-up[t]		●[#]							
Distribution of thermometer		●[#]							
Distribution of pulse oximeter[u]		●[#]							
Distribution of MA-COV form[v]		●[#]							
Training and distribution: mid-turbinate nasal swab kit and saliva recipients		●[#]							
Symptoms of Infection with Coronavirus-19 (SIC), including body temperature measured by the participant (ePROs to be		●[#]							

Phase	Screening[a]	Study Period					Long-term Follow-up		
Visit #[b]	1	2	3	4[c]	5[d]	6	7	8	Exit[e]
Visit Timing		Vac	Vac + 28 d	Vac + 70 d	Vac + 24 w	Vac +52 w	Vac +78 w	Vac +104 w	
Visit Day/Week	Day -28 to 1	Day 1	Day 29	Day 71	Week 24	Week 52	Week 78	Week 104	
Visit Window			±3 d	±3 d	±21 d	±21 d	±28 d	±28 d	
Visit Type	Screening	Vaccination	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Early Exit
completed by the participant in the eCOA)[w]									
Vaccination		●							
Post-vaccination observation[x]		●							
COVID-19 signs and symptoms surveillance[y]		- *Continuous* -							
MAAE recording[z]		- *Continuous* -							
(S)AE recording[aa]		- *Continuous* -							●
Concomitant therapies[bb]		- *Continuous* -							●
Humoral immunogenicity (serum), mL (non-Immuno Subset Participants) [cc]		●[#]10	●10			●10			●[cc]10
IMMUNO SUBSET ONLY									
Humoral immunogenicity (serum), mL[dd]		●[#]15	●15	●15	●15	●15	●15	●15	● [cc]15
SAFETY SUBSET ONLY									
Solicited AE recording[ee]		*Cont +7d*							●[m]
Unsolicited AE recording[ff]		*Cont +28 d*							●[gg]
Ruler training and distribution of ruler[hh]		●							
Participant e-Diary review			●						
Approx. blood draw per visit, mL: 400 participants (Immuno Subset) [Other participants]		17.5 [12.5]	15 [10]	15 [0.0]	15 [0.0]	15 [10.0]	15 [0.0]	15 [0.0]	15 [10]
Approx. cumulative blood draw, mL: 400 participants (Immuno Subset) [Other participants]		17.5 [12.5]	32.5 [22.5]	47.5 [22.5]	62.5 [22.5]	77.5 [32.5]	92.5 [32.5]	107.5 [32.5]	

[#] pre-vaccination

a. Screening will be performed within 28 days prior to the 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 an adequately trained health care professional (HCP), if allowed per local regulations.

c. Visit 4 is only applicable for participants in the Immuno Subset.
d. For non-Immuno Subset participants, Visit 5 can be performed by a phone or telemedicine contact, if allowed by local regulations.
e. For those participants who are unable to continue participation in the study up to Visit 8, 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).
f. 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.
g. Check clinical status again before study vaccination.
h. 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.
i. 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 vaccination must be recorded at screening.
j. 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 Visit 5 is performed by a phone or telemedicine contact, recording of body temperature is not required.
m. If within 7 days of the vaccination.
n. For participants of childbearing potential only.
o. Baseline diagnostic molecular RT-PCR test for SARS-CoV-2 infection will be performed centrally, using a mid-turbinate nasal swab sample. The test will be performed for all participants who are seropositive.
p. Blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity.
q. A screening serologic test for past or current infection with SARS-CoV-2 may be performed in a local lab, only upon request and at the discretion of the sponsor, in areas where seroprevalence is predicted to be high, to restrict the proportion of seropositive participants in the study.
r. MRU over the last 3 months before vaccination will be collected by interview with the participant and recorded in the eCRF.
s. 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.
t. 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.
u. 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).
v. The Medically-attended -COV form (Appendix 8) will be provided to the participant at the vaccination visit and should be completed by the medical care provider during medical visits for COVID-19 or COVID-19 complications.

w. 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.
x. All participants that are not part of the Safety Subset will be closely observed for a minimum of 15 minutes post-vaccination to monitor for the development of any acute reactions. Participants in the Safety Subset will be closely observed for a minimum of 30 minutes post-vaccination. 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.
y. Until 1-year post-vaccination or until the primary analysis takes place (whichever comes last), 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 post-vaccination or after the primary analysis takes place (whichever comes last), until the end of the long-term follow-up period, the frequency of this surveillance question 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. For all participants that are lost to follow-up through eCOA and hospitalization has not been recorded, every effort will be made to document their status.
If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.2 and Section 8.1.2.
z. MAAEs are to be reported for all participants from the moment of vaccination until 6 months after the 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.
aa. 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 (regardless of the causal relationship) are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. Special reporting situations, whether serious or non-serious, are to be recorded 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.
bb. Refer to Section 6.8 for collection and recording of concomitant therapies associated with SAEs, solicited and unsolicited AEs, and MAAEs.
cc. Baseline blood sample for humoral immunity also includes sample for sero-confirmation of SARS-CoV-2 infection. Blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw.
dd. Baseline blood sample for humoral immunity also includes sample for sero-confirmation of SARS-CoV-2 infection. Samples will be collected for 400 participants at selected sites.
ee. 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 time of vaccination until 7 days post-vaccination.
ff. All other unsolicited AEs will be reported for the vaccination from the time of vaccination until 28 days post-vaccination. In order to perform the safety assessment after 2,000 participants have been vaccinated in Stages 1a and 2a, 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.
gg. If within 28 days of the vaccination.
hh. 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 COVID-19-like Signs and Symptoms

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,f]		COVID-19 Day 29 (±7 d)[g,h]
		Part 1[b]	Part 2[c]	1st day of cycle	2nd day of cycle	
Location	**Home[i]**	**Site or Home[j,k]**	**Site or Home[j,k]**	**Home[k]**	**Home[k]**	**Site or Home[j,k]**
Participant to contact study site with any health concerns	●					
Site to contact participant if COVID-19 signs or symptoms are recorded in eCOA	●					
Confirmation of suspected COVID-19 using prespecified criteria	●[l]	●[m]				
Mid-turbinate nasal swab sample (collected by the participant at home)[n]	●[o]			●		
Mid-turbinate nasal swab sample (collected by qualified study staff)		●[p]				
Saliva sample (collected by the participant)[q]			●		●	
Humoral immunity (serum), mL[r]			●15			●15
Biomarker RNAseq blood sample (PAXgene tubes, whole blood), mL[s]			●2.5			●2.5
Symptoms of Infection with Coronavirus-19 (SIC), including highest body temperature over the last 24 hours measured by the participant[t] (ePROs to be completed by the participant in the eCOA)	- - - - - - - - - - - - - - - - - - *Daily* - - - - - - - - - - - - - - -					●
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]	●[o]	- - - - - - - - - *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.
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 1-2.
c. 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 1-2 and COVID-19 Day 3-5 (as assessed during Part 1 of the COVID-19 Day 3-5 visit).
d. Participants should be encouraged by the site to collect nasal swabs and saliva samples as indicated in the Schedule 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.

e. 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 Schedule of Activities, until the end of the study/early withdrawal.
f. 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 mid-turbinate 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.
g. 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 1-2 and COVID-19 Day 3-5, and have at least 1 SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1-2 or Day 3-5.
h. The visit on COVID-19 Day 29 can be combined with a regular study visit if within the applicable visit windows.
i. 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.
j. All COVID-19 Day 3-5 and Day 29 assessments may be performed by an adequately trained HCP at the participant's home, if allowed per local regulations.
k. 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 an adequately 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.
l. 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).
m. 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).
n. 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 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. More details are provided in the laboratory manual. If the participant requires assistance, the participant's caregiver or an adequately trained HCP can help the participant to collect the nasal swabs.
o. 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.
p. For participants with signs or symptoms of COVID-19, confirmation of SARS-CoV-2 infection by the central laboratory will be used for the analysis of the case definition. All nasal swabs may also be tested by a local laboratory for case management.
q. 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. More details are provided in the laboratory manual. If the participant requires assistance, the participant's caregiver or an adequately trained HCP can help the participant to collect the saliva samples.
r. Blood sample for humoral immunity also includes sample for sero-confirmation of SARS-CoV-2 infection.
s. Blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity.
t. 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.

u. Includes measurement of vital signs (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. 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. The results 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 during medical visits for COVID-19 or COVID-19 complications.

Upon closure of the COVID-19 procedures, all participants will fall back to the default Schedule 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.

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 Investigator's Brochure (IB) for Ad26.COV2.S.[33,34]

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".

Study VAC31518COV3001 is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V) in collaboration with Operation Warp Speed (OWS), which also encompasses the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the COVID-19 Prevention Trials Network (COVPN).

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.[17,68] 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.[40,42,69] 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.[3,35,44]

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 initial effort will be to rapidly demonstrate safety and immunogenicity in adults aged ≤55 years in study VAC31518COV1001, in order to initiate the efficacy study VAC31518COV3001 in this age group as soon as possible, and to evaluate safety and immunogenicity in older adults aged ≥65 years. 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.[17,27,45] 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.[71]

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

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[20,64] 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.[42,64] 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.[61,62] 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%).[54] 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.[10,59]

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.[63] 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.[71] 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.[15,71] 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.[15,63] 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[8,52,67,70] and the only viral protein that can elicit protective immunity in

animal models.[5,6,9,51,65] Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen.

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.[2,4,19,44,47,48,50,58,60,66] This type 1 polarity of the immune response is thought to minimize the risk of enhanced disease after SARS-CoV-2 infection.

Study VAC31518COV3001 will include ≥18- to <60-year-old participants and participants ≥60 years of age. Enrollment of adults in these 2 age categories will be initiated in a staggered manner, as described below.

Study VAC31518COV3001 will start with enrollment in Stage 1 (≥18- to <60-year-old participants) based on all available safety and reactogenicity data, and all relevant and available immunogenicity data from Cohort 1a of the first-in-human (FIH) study with the vaccine candidate (Ad26.COV2.S; study VAC31518COV1001; see Section 2.2), immunogenicity data (including Th1 responses) from non-human primates (NHPs), and efficacy in hamsters and NHPs and all other relevant data. Immunogenicity data from Cohort 1a of study VAC31518COV1001 will include virus neutralization assay (VNA), enzyme-linked immunosorbent assay (ELISA) and Th1/Th2 response data.

Stage 2 (participants ≥60 years of age) of study VAC31518COV3001 will start enrolling based on safety, reactogenicity, and immunogenicity data from Cohort 3 of study VAC31518COV1001 (see Section 2.2). Immunogenicity data from Cohort 3 of study VAC31518COV1001 will include VNA, ELISA and Th1/Th2 response data. The Day 3 safety assessment of Stage 1a of VAC31518COV3001 should have been performed with a recommendation to proceed to stage 1b, and there should be no recommendation to halt vaccination of Stage 2 by the DSMB at the time of initiation.

If the post-Dose 1 data from study VAC31518COV1001 do not adequately support initiation of a single-dose vaccination regimen in study VAC31518COV3001, enrollment will not start until post-Dose 2 data from study VAC31518COV1001 are available. If the post-Dose 2 data from study VAC31518COV1001 demonstrate an adequately increased immune response that meets minimum criteria (based on protective levels from NHP, levels in infected people, and from other studies)[33,34] for initiation of a 2-dose vaccination regimen in study VAC31518COV3001, a regimen consisting of 2 doses of Ad26.COV2.S separated by 56 days will be introduced via a protocol amendment.

Within Stage 1 and Stage 2, enrollment will be restricted to participants without comorbidities that are associated with increased risk of progression to severe COVID-19 as described below.

The study will start by enrolling 2,000 participants (≥18- to <60-year-old) without comorbidities that are associated with increased risk of progression to severe COVID-19 (including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients) (Stage 1a of the study), then vaccination will be paused to allow the Data Safety Monitoring Board (DSMB) to examine 3-day safety data (consisting of Grade 4 adverse events [AEs] and serious adverse events [SAEs] [including those from the ongoing Phase 1/2 studies]). If no safety concerns are identified, enrollment will proceed, expanding enrollment to ≥18- to <60-year-old participants with comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 1b) (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).

In Stage 2 of the study, the first 2,000 adults ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (Stage 2a; including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients). Following enrollment of these initial 2,000 participants in Stage 2a, further vaccination in Stage 2 of the study will be paused to allow the DSMB to examine 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from Stage 1 and the ongoing Phase 1/2 studies]). Upon confirmation that there are no safety concerns in this population or in the Stage 1 population up to that point, enrollment will proceed, also including participants aged ≥60 years with comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 2b) (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 (including ≥18- to <60-year-old and ≥60-year-old participants, and participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19) will be 30,000 to 60,000 participants. It is intended that a minimum of approximately 25% of recruited participants will be ≥60 years of age. If prior study results do not support initiation of Stage 2 (≥60-year-old participants), the study will be limited to Stage 1 (≥18- to <60-year-old participants) up to the targeted sample size. Under these circumstances, a protocol amendment may be created to modify the study to introduce a 2-dose regimen of Ad26.COV2.S in the participants ≥60 years of age, if the data generated by the 2-dose vaccination regimen in Cohort 3 of study VAC31518COV1001 demonstrate an immune response that meets criteria for initiating study VAC31518COV3001 in participants ≥60 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, up to a maximum of 60,000 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. The sample size may be adjusted by the Sponsor Committee during the study, based on blinded data, to ensure sufficient power at the time of the primary analysis (PA). 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

No clinical data with the Ad26.COV2.S vaccine are currently available.

The FIH study VAC31518COV1001 will be ongoing at the time of initiation of study VAC31518COV3001. 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 1b). In addition, safety, reactogenicity, and immunogenicity will be evaluated in a cohort of adults aged ≥65 years. Overall, a target of 1,045 adult participants in these 2 age groups will be randomly assigned in this study.

The study includes the following cohorts (Table 1):

1. Cohort 1:
    a. Cohort 1a: 375 participants (75 participants per group) aged ≥18 to ≤55 years who will be randomized in parallel in a 1:1:1:1:1 ratio to 1 of 5 vaccination groups.
    b. Cohort 1b: 25 participants (5 participants per group) aged ≥18 to ≤55 years who will be enrolled at the Beth Israel Deaconess Medical Center (BIDMC) and randomized in parallel in a 1:1:1:1:1 ratio to 1 of 5 vaccination groups. Additional exploratory immunogenicity evaluations (eg, epitope mapping, passive transfer, and certain analyses of functional and molecular antibody characteristics) will be performed for Cohort 1b.
2. Cohort 2: 270 participants aged ≥18 to ≤55 years will be randomized to receive Ad26.COV2.S (240 participants) or a placebo (30 participants) in the primary regimen. Cohort 2 will include an evaluation of a single booster vaccination.
3. Cohort 3: 375 participants (75 participants per group) aged ≥65 years who will be randomized in parallel in a 1:1:1:1:1 ratio to 1 of 5 vaccination groups.

Table 1: Vaccination Schedules of Study VAC31518COV1001

Cohort 1a (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	75	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
2	75	Ad26.COV2.S 5×10^{10} vp	Placebo
3	75	Ad26.COV2.S 1×10^{11} vp	Ad26.COV2.S 1×10^{11} vp
4	75	Ad26.COV2.S 1×10^{11} vp	Placebo
5	75	Placebo	Placebo
Cohort 1b (Adults ≥18 to ≤55 years) [a]			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	5	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
2	5	Ad26.COV2.S 5×10^{10} vp	Placebo
3	5	Ad26.COV2.S 1×10^{11} vp	Ad26.COV2.S 1×10^{11} vp
4	5	Ad26.COV2.S 1×10^{11} vp	Placebo
5	5	Placebo	Placebo
Cohort 2a (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)** [b]	**Day 57** [b]
1-4	120	Ad26.COV2.S 1×10^{11} vp	No vaccination
5	15	Placebo	No vaccination
Cohort 2b (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)** [b]	**Day 57 (Vaccination 2)** [b]
1-4	120	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
5	15	Placebo	Placebo
Cohort 3 (Adults ≥65 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	75	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
2	75	Ad26.COV2.S 5×10^{10} vp	Placebo
3	75	Ad26.COV2.S 1×10^{11} vp	Ad26.COV2.S 1×10^{11} vp
4	75	Ad26.COV2.S 1×10^{11} vp	Placebo
5	75	Placebo	Placebo
Total	**1,045**		

a. Cohort 1b comprises 5 participants in each group who will be enrolled at Beth Israel Deaconess Medical Center (BIDMC) and for whom additional exploratory immunogenicity analyses will be performed.

b. Study vaccine will be administered as a single-dose (Day 1) or 2-dose (Day 1 and Day 57) primary regimen. Cohort 2 will also include an evaluation of a single booster vaccination at 6, 12, or 24 months after completion of the primary single-dose or 2-dose primary regimen.

N = number of participants; vp = virus particles.

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.[46] 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 reminiscent of 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 VAC31518COV3001 protocol.

For the most comprehensive nonclinical information regarding Ad26.COV2.S, refer to the latest version of the IB.[33,34]

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 and do not require treatment.

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 vaccination, participants will remain at the study site for close observation by study staff to monitor for the development of any acute reactions. All participants that are not part of the Safety Subset will be observed for at least 15 minutes post-vaccination, while Safety Subset participants will be observed for at least 30 minutes post-vaccination. Necessary emergency equipment and medications must be available in the study site to treat severe allergic reactions.

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

[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.

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 study vaccine (see Section 5.1). Participants who are pregnant or breastfeeding will be excluded from the study. Participants who become pregnant during the study 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.

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 Mid-turbinate Nasal Swab Samples

Collection of a nasal swab sample may cause a nosebleed.

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 (Stage 1). As a risk mitigation strategy, all participants in the study will be passively and actively monitored for acquisition of molecularly confirmed COVID-19 (see Section 4.1 and Section 8.1.2). This active and passive surveillance system for detection of COVID-19, with influenza serving as a control to monitor the effectiveness of the surveillance system, will ensure rapid identification of COVID-19 and will ensure that appropriate treatment procedures can be initiated to reduce the risk of enhanced disease if it should occur. 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 DSMB 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 DSMB 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.
  - After vaccination, participants will remain at the study site for at least 15 to 30 minutes (not part of Safety Subset versus Safety Subset, respectively) and will be closely observed by study staff to monitor for the development of any acute reactions. 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.
  - A DSMB 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 DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter. The DSMB will also review 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from the ongoing Phase 1/2 studies]) from participants enrolled in Stages 1a and Stage 2a, before enrollment of

participants in Stages 1b and Stage 2b, respectively. 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:
    - The study will initially enroll ≥18- to <60-year-old participants (Stage 1 of the study) based on immunogenicity and safety data from Cohort 1a of study VAC31518COV1001 (see details in Section 2.1). In Stage 1a, 2,000 participants without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients), then vaccination will be paused to allow the DSMB to examine 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those the ongoing Phase 1/2 studies]). If no safety concerns are identified, enrollment will proceed, also including ≥18- to <60-year-old participants with comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 1b) (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).
    - In Stage 2 of the study, first 2,000 adults ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (Stage 2a; including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients) based on the immunogenicity and safety data from Cohort 3 of study VAC31518COV1001 and emerging safety data from Stage 1 of study VAC31518COV3001 (see details in Section 2.1). Following enrollment of the initial 2,000 participants aged ≥60 years (Stage 2a), further vaccination in Stage 2 of the study will be paused to allow the DSMB to examine 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from Stage 1 and the ongoing Phase 1/2 studies]). Upon confirmation that there are no safety concerns in this population or in the Stage 1 population up to that point, enrollment will proceed, also including participants aged ≥60 years with comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 2b) (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, follow and potentially treat COVID-19, 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 Stages 1a and 2a, that if met would result in pausing of further vaccinations (see Section 6.9), preventing exposure of new participants to

study vaccine until the DSMB 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 28 days post-vaccination
Secondary *(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 post-vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 28 days post-vaccination
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b] in SARS-CoV-2 seronegative adults, as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day post-vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) or linked to any molecularly confirmed[a], COVID-19[b,c] at least 28 days post-vaccination
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
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 28 days post-vaccination

Objectives	Endpoints
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 28 days post-vaccination
To assess the effect of Ad26.COV2.S on all molecularly confirmed[a] symptomatic COVID-19[b,c], as compared to placebo	First occurrence of molecularly confirmed[a] COVID-19[b,c] (any severity) at least 28 days post-vaccination
To assess the effect of Ad26.COV2.S on occurrence of asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline and 1 year post-vaccination using an ELISA and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
Safety	
To evaluate safety in terms of SAEs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship to vaccination of SAEs (during the entire study), MAAEs (until 6 months post-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 vaccination, and in terms of unsolicited AEs during 28 days post-vaccination	Occurrence, intensity, duration and relationship to vaccination of solicited local and systemic AEs during 7 days after vaccination and of unsolicited AEs during 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	– Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA – SARS-CoV-2 neutralization as measured by VNA (wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein)
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 28 days post-vaccination
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 28 days after vaccination with study vaccine
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection in participants with comorbidities associated with	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-

Objectives	Endpoints
increased risk of progression to severe COVID-19, as compared to placebo	19 with onset at least 28 days after vaccination with study vaccine
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 28 days after vaccination with study vaccine
To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo	Deaths occurring at least 28 days after vaccination with study vaccine
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, as well as gene transcript profiling (RNA sequencing), 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 – 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

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result 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)

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 28 days after the 1st vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, 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 to <60 years of age and ≥60 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 study vaccine.

The study will consist of a screening phase of up to 28 days, a 52-week double-blind study period (including the administration of 1 dose of study vaccine [on Day 1], 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 1 month. 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 intramuscular (IM) injections of Ad26.COV2.S or placebo as shown in Table 2. Ad26.COV2.S will be administered at a dose level of 1×10^{11} vp.

Table 2: Vaccination Schedule VAC31518COV3001

Group	N	Day 1
1	Up to 30,000	Ad26.COV2.S (1×10^{11} vp)
2	Up to 30,000	Placebo

N = number of participants; vp = virus particles.
Note: It is intended that a minimum of approximately 25% of recruited participants will be ≥60 years of age

A staggered enrollment strategy will be used:

- Stage 1a: Initially, 2,000 participants (≥18- to <60-year-old) without comorbidities that are associated with increased risk of progression to severe COVID-19 (including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients) will be enrolled based on acceptable Day 29 safety and adequate immunogenicity data, including Th1/Th2, from the corresponding age group (Cohort 1a) of the FIH study VAC31518COV1001 (see Section 2.2 for more details).
- Stage 1b: After a vaccination pause, to allow the DSMB (also known as an independent data monitoring committee [IDMC]) to examine 3-day safety data (consisting of Grade 4 AEs and all SAEs, [including those from the ongoing Phase 1/2 studies]) and if no safety concerns are identified enrollment will proceed, expanding enrollment to include≥18- to <60-year-old participants with comorbidities that are associated with increased risk of progression to severe COVID-19 (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).
- Stage 2a: Based on acceptable Day 29 safety and adequate immunogenicity (Th1/Th2) data from Cohort 3 of the FIH study VAC31518COV1001 (see Section 2.2 for more details) and emerging safety data from Stage 1 of this Phase 3 study, 2,000 participants ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including 1,000 Ad26.COV2.S recipients and 1,000 placebo recipients).
- Stage 2b: After a vaccination pause (in the age group ≥60 years of age) to examine the 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from Stage 1 and the ongoing Phase 1/2 studies]) from Stage 2a by the DSMB, if no safety concerns are identified in this population, enrollment will proceed, also including participants aged ≥60 years with comorbidities that are associated with increased risk of progression to severe COVID-19(see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities). Once initiated, Stage 2 may run in parallel with Stage 1 and will enroll a minimum of approximately 25% of the total study population.

If the post-Dose 1 data from study VAC31518COV1001 do not adequately support initiation of a single-dose vaccination regimen in study VAC31518COV3001, enrollment will not start until post-Dose 2 data from study VAC31518COV1001 are available. If the post-Dose 2 data from study VAC31518COV1001 demonstrate an adequately increased immune response that meets minimum criteria (based on protective levels from NHP, levels in infected people, and from other studies)[33,34] for initiation of a 2-dose vaccination regimen in study VAC31518COV3001, a regimen consisting of 2 doses of Ad26.COV2.S will be introduced via a protocol amendment.

Overall, a target of 30,000 to 60,000 adult participants (≥18- to <60-year-old and ≥60-year-old, 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, including in the ≥18- to <60-year-old population. The intent is to have a COVID-19 incidence in the study higher than 1% so that the sample size and enrollment period can be reduced. The actual sample size for the study, up to a maximum of 60,000 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. The sample size may be adjusted by the sponsor Committee during the study, based on blinded data, to ensure sufficient power at the time of the PA. Details on the possible blinded sample-size reassessment will be described in the SAP. 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 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 DSMB. 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 description in Section 9.5.1.

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 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). Biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity will also be studied (see Section 8.5). Medical resource utilization (MRU) following vaccination will be recorded for all participants with molecularly confirmed, symptomatic COVID-19 (see Section 8.6).

After vaccination, all participants that are not part of the Safety Subset will remain under observation at the study site for at least 15 minutes to monitor for the development of any acute reactions. Participants in the Safety Subset will be closely observed for a minimum of 30 minutes post-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 study vaccination to monitor for signs and symptoms of COVID-19 (to determine duration of protection) and to monitor for safety. 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 Immuno Subset will additionally 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 adult inflammatory syndrome, pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death)[61], and for MRU (such as rates of ICU admission, ventilator use).

Until 1 year post-vaccination or until the primary analysis takes place (whichever comes last), 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 post-vaccination or after the primary analysis takes place (whichever comes last), until the end of the long-term follow-up period, the frequency of this surveillance question through the eCOA will decrease to once every 2 weeks. For all participants that are lost to follow-up through eCOA and hospitalization has not been recorded, every effort will be made to document their status.

All participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19 (see Section 8.1.1) on COVID-19 Day 1-2 and Day 3-5 should undertake the COVID-19 procedures (see Section 8.1.2 and Section1.3) until 14 days after symptom onset (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last, unless 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 the 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's medical care provider will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

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).

A DSMB 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).

Biomarker Collection

For participants with a positive test result for SARS-CoV-2 infection, biomarker analysis (PAXgene, RNAseq) will be performed to explore potentially informative biomarkers, eg, those associated with severe COVID-19.

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.

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. 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.[54,55]

4.3. Justification for Dose

The dose level of Ad26.COV2.S to be assessed in the present study (1×10^{11} 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 1×10^{11} vp is the highest 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 will also be assessed in study VAC31518COV1001.

Non-human primates immunized with a single-dose of Ad26.COV2.S at 1×10^{11} vp (Study 20-09) showed robust protection after intranasal and intratracheal challenge with SARS-CoV-2. Ad26.COV2.S provided complete protection in 5 of 6 animals, whereas 1 animal had low levels of virus in the upper respiratory tract. All control animals showed substantial viral load in both the lower and upper respiratory tract.

The 1×10^{11} 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 104 weeks post-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 administration of the study vaccine, or on the day of the 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 (1a, 1b, 2a, and/or 2b), 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 (or their legally acceptable representative based on local regulations) 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. **Stages 1a and 1b:** Participant is ≥18 to <60 years of age on the day of signing the ICF.

   As of Stages 2a and 2b: Participant is ≥60 years of age on the day of signing the ICF.
4. **Stages 1a and 2a:** 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 Criteria 15), as long as their symptoms and signs are stable and well-controlled. If participants are on medication for a condition, the medication dose must have been stable for at least 12 weeks preceding vaccination and expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and height and weight measurement at screening.

As of Stages 1b and 2b: In the investigator's clinical judgement, participant may have a stable and well-controlled comorbidity associated with an increased risk of progression to severe COVID-19.[13] If participants are on medication for a condition, the medication dose must have been stable for at least 12 weeks preceding vaccination and expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and height and weight measurement at screening.

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. 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 administration of study vaccine. Use of hormonal contraception should start at least 28 days before the administration of study vaccine. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the vaccination. Acceptable effective methods 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/litigation 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 receiving study vaccine.*

[a]The study will remain consistent with any new information, as indicated by the US CDC. In this study, (former) smoking will not be considered as a comorbidity.

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 study vaccine administration.
7. Participant agrees to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving 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]).

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 study vaccination; 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. Participant has abnormal function of the immune system resulting from:
   a. Clinical conditions (eg, autoimmune disease, potential immune mediated disease or known or suspected immunodeficiency, chronic kidney disease [with dialysis]) 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 (>10 days) or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg/kg body weight 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 study vaccine and during the study.

4. Participant received treatment with Ig in the 3 months or blood products in the 4 months before the planned administration of the 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 study vaccine.
   b. Other licensed (not live) vaccines - within 14 days before or after planned administration of study vaccine.
6. Participant previously received a coronavirus vaccine.
7. Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the 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.
8. Participant is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after 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. Participants with HIV infection, which is not well-controlled in the judgement of the investigator, with or without highly active antiretroviral therapy.
12. Participant has had major psychiatric illness or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.
13. Participant cannot communicate reliably with the investigator.
14. 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.
15. **Stages 1a and 2a:** 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

[a]The study will remain consistent with any new information, as indicated by the US CDC. In this study, (former) smoking will not be considered as a comorbidity.

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, type 2, or gestational); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and (pulmonary) hypertension or high blood pressure; obesity (body mass index [BMI] $\geq$30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; sleep apnea; Parkinson's disease; seizures; ischemic strokes; Intracranial hemorrhage; Guillain-Barré syndrome; encephalopathy; meningoencephalitis; and participants who live in nursing homes or long-term care facilities. For details and exceptions, refer to the exclusion criteria in Section 5.2.

16. **Stages 1a and 2a:** 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).
17. **Stages 1a and 2a:** Participant has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).
18. **Stages 1a and 2a:** Participant had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization, or has surgery requiring hospitalization planned during the time the participant is expected to participate in the study or within 6 months after study vaccine administration.
19. **Stages 1a and 2a:** 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 study vaccination. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the study vaccination 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.

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 participant in Stages 1a or 2a, but does meet the criteria for participation in Stages 1b or 2b, will not be considered a screening failure and can be enrolled in the appropriate stage.

An individual who does not meet the criteria for participation in this study (screen failure) may be rescreened on 1 occasion only. 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:

- 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 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.

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1. Study Vaccines Administered

Ad26.COV2.S will be supplied at a concentration of 2×10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dosed at 1×10^{11} vp. Placebo is 0.9% NaCl.

For blinding purposes, all participants will receive Ad26.COV2.S or placebo at Day 1 (see Schedules of Activities), using the same volume (ie, 0.5 mL).

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 (2×10^{11} vp/mL)	0.9% Sodium Chloride
Type	Biologic/vaccine (1 dose)	Placebo (1 dose)
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 2×10^{11} vp/mL	0.9% NaCl
Dosage Level(s)	**Day 1**: Ad26.COV2.S (1×10^{11} vp)	**Day 1:** 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 who will perform the injection. An unblinded study-site pharmacist, or other qualified individual, may also perform the vaccination but will have no other study function following vaccination.

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 15.

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, biomarker, 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 DSMB 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.

6.4. Study Vaccine Compliance

Study vaccines will be administered intramuscularly by a study vaccine administrator – a trained and qualified study nurse, medical doctor, or otherwise qualified HCP. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing. The date and time of 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

A plan will be developed in accordance with local and national regulations and in consultation with Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) involved in the study and responsible national authorities, to determine conditions under which it is recommended that those participants that received placebo vaccine may be vaccinated with active study vaccine after efficacy of the degree determined necessary by the agreed upon plan has been demonstrated. It is the preference that duration of protection be determined for this vaccine in order to determine the vaccine's utility and that placebo participants will not be vaccinated until at least 1 year after initial vaccination and preferably not until the end of the study. The consent form will inform all potential volunteers that this is our intent, if feasible.

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 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 vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after 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 vaccination through 28 days after vaccination. Concomitant therapies associated with solicited AEs will be collected by the participants and recorded in the eCRF from the time of vaccination through 7 days after vaccination.

Participants may not receive an investigational drug (including investigational drugs for prophylaxis of COVID-19) or use an invasive investigational medical device within 30 days or receive an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration 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 study vaccine in order to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Chronic (>10 days) or recurrent use of systemic corticosteroids[a] and administration of antineoplastic and immunomodulating agents or radiotherapy are prohibited during the study and within 6 months before the planned administration 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 Stages 1a and 2a

A committee consisting of the representatives of the sponsor and collaboration partners, along with the principal investigator (the protocol safety review team [PSRT]) will monitor safety in a blinded manner, including the study vaccination pausing rules (applicable to Stages 1a and 2a only).

The occurrence of any of the following events in Stages 1a and 2a 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 PSRT then decides whether a study pause is warranted. 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 DSMB members and coordination of a DSMB meeting in the event of a study pause.

The DSMB 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 DSMB. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. The formal recommendation from the

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

DSMB 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.

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 DSMB 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 DSMB, participant safety may be threatened.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Not applicable

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
- 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 mid-turbinate 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 107.5 mL for participants in the Immuno Subset and 32.5 mL for the other participants. Additional blood samples (up to 35 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.

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.

The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination.

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 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 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.

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
- Mid-turbinate 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:

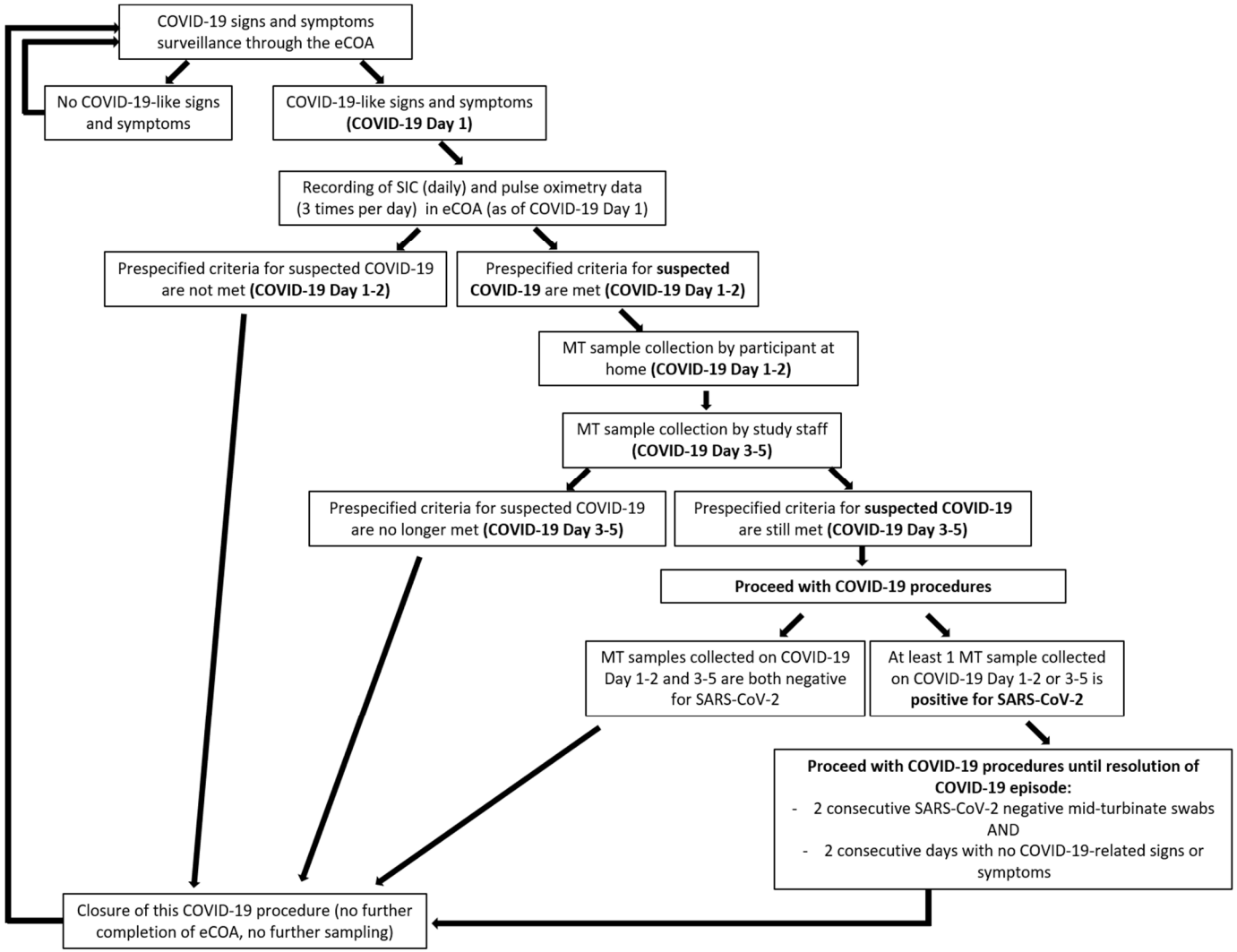
New onset or worsening of any 1 of these symptoms, which lasts for at least 24 hours, not otherwise explained:

- 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

8.1.2. Procedures in the Event of COVID-19-like Signs and Symptoms

Procedures to be performed in the event a participant experiences signs or symptoms suggesting possible COVID-19 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; MT = mid-turbinate; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19.

Until 1 year post-vaccination or until the primary analysis takes place (whichever comes last), 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 post-vaccination or after the primary analysis takes place (whichever comes last), until the end of the long-term follow-up period, the frequency of this surveillance question 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. For all participants that are lost to follow-up through eCOA and for whom hospitalization has not been recorded, every effort will be made to document their status. 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.

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. More 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). 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 complete the ePROs in the eCOA:
  - 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, the participant's caregiver or an adequately 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.
- The participant will be asked to come to the site on **COVID-19 Day 3-5** (between 2 and 4 days after symptom onset).
  - If a site visit is not feasible, a member of the study staff could visit the participant at home (or at the hospital or other location, if needed), if allowed by local regulations. The COVID-19 Day 3-5 assessments may also be performed by an adequately trained HCP, if allowed per local regulations.
  - During **Part 1** of the **COVID-19 Day 3-5** visit, 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, 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. Also, a nasal swab for detection of SARS-CoV-2 and exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity will be collected by a qualified member of the study site.
  - If the prespecified criteria for suspected COVID-19 are still met on COVID-19 Day 3-5, 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 and exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity 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 the prespecified criteria for suspected COVID-19 are no longer met on COVID-19 Day 3-5, the participant will not undertake any further COVID-19 procedures. He/she will fall back to the default Schedule of Activities, until the end of the study/early withdrawal.

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

- The participant will be reminded to further complete the ePROs in the eCOA:
  - The SIC questionnaire, 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 SIC should be recorded by site staff in the clinical database.
- The participant 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, the participant's caregiver or an adequately 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. More details are provided in the laboratory manual.

  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.

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 Schedule 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 AND has met the prespecified criteria for suspected COVID-19 on COVID-19 Day 1-2 and Day 3-5, then the participant 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[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 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.

If a participant has at least 1 SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1-2 or Day 3-5 AND has met the prespecified criteria for suspected COVID-19 on COVID-19 Day 1-2 and Day 3-5, 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 and exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity. 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. The participant will complete the SIC (Appendix 6) in the eCOA.

Note: if for any reason a site visit is not feasible, a member of the study staff can visit the participant at home (or at the hospital or other location, if needed), if allowed by local regulations. The COVID-19 Day 29 assessments may also be performed by an adequately trained HCP at the participant's home, if allowed per local regulations.

Note: this visit can be combined with a regular study visit if within the applicable visit windows.

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 vaccination visit and should be completed by the medical care provider during medical visits for COVID-19 or COVID-19 complications.

Upon closure of the COVID-19 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.

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

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 COVID-19 and Section 8.1.3.2 for Case Definition of Mild COVID-19.

Molecular confirmation of SARS-CoV-2 infection by the 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 8.1.3.4). 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 adult inflammatory syndrome, pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death)[61] 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 (pre-vaccination) and at 1 year after vaccination).

8.1.3.1. Case Definition for Moderate to Severe 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:

- Any 1 of the following new or worsening signs AND any 1 of the following new or worsening symptoms:

Signs	Symptoms
Respiratory rate ≥20 breaths/minute	Shortness of breath (difficulty breathing)
Abnormal saturation of oxygen (SpO_2) but still >93% on room air at sea level*	Fever (≥38.0°C or ≥100.4°F)
Heart rate ≥90 beats/minute	Cough
Clinical or radiologic evidence of pneumonia	Sore throat
Radiologic evidence of deep vein thrombosis (DVT)	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)

* SpO_2 criteria will be adjusted according to altitude.

OR

- Any 2 of the following new or worsening symptoms:

Fever (≥38.0°C or ≥100.4°F)
Shaking chills or rigors
Cough
Shortness of breath (difficulty breathing)
Sore throat
Malaise as evidenced by 1 or more of the following elements*: - Loss of appetite - Generally unwell - Fatigue - Physical weakness
Headache

Muscle pain (myalgia)

Gastrointestinal symptoms as evidenced by 1 or more of the following elements*:

- diarrhea
- vomiting
- nausea
- abdominal pain

Red or bruised looking feet or toes

New or changing olfactory or taste disorders

* 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:

- 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.

- 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:

- 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, or chills, without shortness of breath or dyspnea.

A case is considered clinically mild when it meets the above case definition but not the moderate to severe 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 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. 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, 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-Immuno Subset participants for humoral immunogenicity assessments before vaccination, 28 days after vaccination, and at 1 year after vaccination.

For a total of approximately 400 participants in the Immuno Subset (ie, participants at sites with access to appropriate processing facilities), blood will be collected for analysis of humoral immune responses before vaccination, 28 days after vaccination, 70 days after vaccination, and 24, 52, 78, and 104 weeks after vaccination.

Participants in the Immuno Subset will be divided into 4 groups as presented in Table 3.

Table 3: Sample Size and Distribution of the Immuno Subset Between Active and Placebo Groups

Study Vaccine	Subset 1a	Subset 1b	Subset 2a	Subset 2b
1×10^{11} vp	50	50	50	50
Placebo	50	50	50	50
Total	**100**	**100**	**100**	**100**

vp = virus particles
Subset 1a: healthy ≥18- to <60-year-old adults without relevant comorbidities, enrolled during Stage 1a.
Subset 1b: ≥18- to <60-year-old adults with relevant comorbidities, enrolled during Stage 1b.
Subset 2a: healthy ≥60-year-old adults without relevant comorbidities, enrolled during Stage 2a.
Subset 2b: ≥60-year-old adults with relevant comorbidities, enrolled during Stage 2b.

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 4.

Table 4: Immunogenicity and Transcriptomic Assays

Humoral Assays	**Purpose**
Secondary Endpoints	
SARS-CoV-2 binding antibodies to S protein (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing 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
Exploratory Endpoints	
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
Antibodies to the RBD of the SARS-CoV-2 S protein (ELISA)	Analysis of antibodies binding to the RBD of the SARS-CoV-2 S protein
Transcriptomic Assay	**Purpose**
Exploratory endpoints	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in unstimulated cells or whole blood

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

A screening serologic test for past or current infection with SARS-CoV-2 may be performed in a local lab, only upon request and at the discretion of the sponsor, in areas where seroprevalence is predicted to be high, to restrict the proportion of seropositive participants in the study.

A baseline serologic test for past or current infection with SARS-CoV-2 will be performed for all participants. Samples for the baseline serologic tests will be sent to the central lab for testing.

8.2. Safety Assessments

Details regarding the DSMB 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 time points provided in the Schedules of Activities.

The PSRT will monitor safety in a blinded manner.

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 an adequately trained HCP, 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.

Participants in the Safety Subset will utilize an e-Diary to record body temperature measurements from the time of vaccination until 7 days post-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 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 supine 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.

8.2.3. Pregnancy Testing

A urine pregnancy test for participants of childbearing potential will be performed at screening and before 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, surrogate, or the participant's legally acceptable representative) 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 vaccination will be collected on the Medical History eCRF page as pre-existing conditions.
- All SAEs and all AEs leading to study discontinuation (regardless of the causal relationship) are to be reported from the moment of 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 vaccination until 6 months after the 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 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 vaccination until 7 days post-vaccination.
- All other unsolicited AEs, whether serious or non-serious, will be recorded from the time of vaccination until 28 days post-vaccination.

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 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.

After vaccination, all participants that are not part of the Safety Subset will remain under observation at the study site for at least 15 minutes to monitor for the development of any acute reactions. Participants in the Safety Subset will remain under observation at the study site for at least 30 minutes post-vaccination.

In addition, participants in the Safety Subset will record solicited signs and symptoms in an e-Diary from time of vaccination until 7 days post-vaccination. 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 post-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 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 post-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 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

Respiratory tract infections reported as a non-serious AE, as well as COVID-19-related Grade 4 AEs and SAEs reported during the course of the study, will be excluded from the AE analyses if the molecular test is subsequently found to be positive for SARS-CoV-2.

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.

8.5. Biomarkers

During a COVID-19 episode, blood will be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 for evaluation of biomarkers (eg, those associated with severe COVID-19).

8.6. 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 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 vaccination visit and should be completed by the medical care provider 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 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)

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). This analysis will take place 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).

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

3. The end-of-study analysis will be performed when all participants have completed the visit 24 months post-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%.
- 90% power to reject a null hypothesis of H0: VE≤30%.
- α at 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 method 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 in Section 8.1.3.1 in the PP population at least 28 days after vaccination with study vaccine.

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. To that end, this protocol reflects the range of sample sizes that could be employed to attain the design assumptions above. The maximum sample size equals 30,000/group (60,000 in total) and is determined based on estimated annualized incidence rate of 1% to 4% at the start of the study to reach the requirements for efficacy evaluation within the targeted time frames, as detailed above.

The sample size will be selected to have a high probability (80-90%) to reach an efficacy signal within 4-6 months after first subject vaccinated for an assumed VE≥70%. Table 5 illustrates the sample sizes required for 3 scenarios of incidence rates. Under those assumptions, the study has 90% probability to reach an efficacy signal within 3 months for an assumed VE=90% and within 6-8 months for an assumed VE=65%.

Table 5: Sample Size

Incidence assumptions for timelines	25,000/group	15,000/group	10,000/group
Oct -Dec 2020	0.35% 1.4% annualized	0.58% 2.33% annualized	0.875% 3.5% annualized
Jan 2021	Reduction by 50%	Reduction by 50%	Reduction by 50%
Feb 2021 onwards	Reduction by 62%	Reduction by 62%	Reduction by 62%

TNE: 104 events
Recruitment 8 weeks, time to operationalize not included, 5% seroprevalence

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. Immuno Subset

All participants included in the Immuno Subset (N=400) will be added randomly at each stage of the staggered enrollment. Healthy adults (Subset 1a) will be enrolled in Stage 1a, adults with comorbidities (Subset 1b) in Stage 1b, healthy elderly (Subset 2a) in Stage 2a, and elderly with comorbidities (Subset 2b), with approximately 100 participants per group as displayed in Table 3.

A sample size of 400 participants, distributed as described in Table 3, 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 non-infected and seronegative non-infected), if feasible.

Controls will be matched with cases from same stage (age, comorbidities) 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 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 post-vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study. Based on a sample size of 60,000 participants, and approximately 30,000 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 6 shows the probabilities of observing at least 1 event (solicited, unsolicited, or SAE) in 1 of the arms at given true AE rates.

Table 6: Probability of Observing at Least 1 Adverse Event or Serious Adverse Event at a Given True Adverse Event Rate in the Active Arm (With a Total Sample Size of 30,000 or 60,000 Participants)

True AE Rate	Probability of Observing at Least 1 Adverse Event on Active in N Participants		
	Solicited/Unsolicited AEs N=3,000	SAEs N=15,000	SAEs N=30,000
0.01%	26%	78%	95%
0.1%	95%	100%	100%
≥0.5%	100%	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 a 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: Participants in the FAS who receive study vaccine and who are seronegative at the time of vaccination 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: All randomized and vaccinated participants, including those who are part of the Immuno 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 Immuno 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.

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

28 days after vaccination 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.

Monitoring for efficacy will start from the 20th event onward by the SSG of the DSMB until the prespecified boundary has been crossed. This boundary is set up using the fully sequential design and is derived in such a way to have 90% power to detect a VE=65% using a one-side alpha=0.025 against H0:VE≤30%. The PA will be triggered when the TNE of 104 is reached or earlier when this prespecified super-efficacy boundary or non-efficacy has been met (evaluating events with start 28 days after 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 the prespecified boundary is met, the SSG will inform the DSMB and, if deemed appropriate by the DSMB, a meeting with the DSMB 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 (both age groups with and without comorbidities) to evaluate the primary and secondary objectives. In addition, these will be supplemented with a subgroup analysis for age group (18 to 60 years, ≥60 years) and comorbidities employing a descriptive summary including 95% confidence intervals to describe the VE in each subpopulation. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (>70 years, >80 years).

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 vaccination, as well as with onset 14 days after vaccination.

9.5.1.1. Study Monitoring

Table 7: 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.	Constant p-value cut-off controlling α at 5%	After every event starting from the 8th event
Non-efficacy	FAS in seronegatives only	H_0: VE ≥40% vs. H_1: VE <40%	Exact 95% CI	Lower limit of the 95%CI <0% and Upper limit of the 95%CI <40%	Every 2 weeks, starting from the 20th event after 28 days post-dose 1[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 28days post-dose 1 are observed, **then after each subsequent event**

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.
[b] Monitoring stops when the primary efficacy analysis is triggered.

All boundaries will be monitored by an SSG. Once a boundary has been crossed, the SSG will inform the DSMB and a DSMB 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 DSMB 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 $H1: rr = rr$ 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

To evaluate the effect of the vaccine against symptomatic, molecularly confirmed COVID-19, including mild infections, the endpoint will evaluate the first occurrence of molecularly confirmed, symptomatic COVID-19 including mild, moderate to severe/critical case definitions in Section 8.1.3.1 and 8.1.3.2, with onset at least 28 days after vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events across age groups, with and without comorbidities.

Furthermore, to evaluate whether the vaccine has an effect on severity of the infection, all participants will be categorized according to the worst observation during the study period as having either no infection, asymptomatic infection, and symptomatic infections: participants' infections will be further categorized as either mild, moderate, or severe. An analysis will be done tabulating the distribution of events in each category in the vaccinated and placebo groups.

All VE evaluations will be repeated regardless of their serostatus.

The statistical analysis for secondary endpoints and multiple testing strategy to evaluate the secondary objectives 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, additional analyses (including using subgroups/covariates) may be performed.

9.5.4. Other Analyses

Biomarkers Analyses

Exploratory biomarker analyses will be part of a separate report.

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. Immuno 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 Immuno 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. More 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 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.

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 post-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 time point 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 time point. 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 time point. 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 Committee(s)

The study will be formally monitored by a DSMB (also known as an IDMC). In general, the DSMB 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 1a (2,000 participants) and stage 2a (2,000 participants). The DSMB will review unblinded data. The DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter.

The DSMB will also review 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from the ongoing Phase 1/2 studies]) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

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 COVID-19 disease/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 disease or death in the vaccine arm compared to the placebo arm starts at the 8th event and at each additional event until the harm boundary is reached or until the end of the study. If the stopping boundary is met, then the SSG immediately informs the Chair of the DSMB through secure communication procedures. At this point the DSMB 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 DSMB will formally monitor the SARS-CoV-2 events to conclude both non-efficacy and efficacy. The DSMB will evaluate in an unblinded fashion whether superiority is established for the primary endpoint or whether non-efficacy is shown (see also Section 9.8) 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 FAS set will be reached. Two versions of the non-efficacy monitoring report will be generated. A report provided to the DSMB 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 and decide on potential blinded sample size reassessment to be able to reach the TNE, the DSMB 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 9.8).

The above high-level rules are preliminary and subject to fine-tuning based on operating characteristics.

Monitoring rules will be formally finalized prior to study start and fully documented in the DSMB SAP.

The SAP will describe the planned analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	adenovirus type 26
AdVac®	adenoviral vaccine
AE	adverse event
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
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
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
PSRT	protocol safety review team
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.[56,57]
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 Safety Laboratory Assessments

Laboratory Assessments	Parameters	Timepoints
Testing done locally	• Urine pregnancy testing for participants of childbearing potential only	• At screening and before 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)	• 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 (mid-turbinate sample collected by the participant at home)
	• Serology blood sample for sero-confirmation of SARS-CoV-2 infection	• At screening, (prior to vaccination) (only upon request and at the discretion of the sponsor)
Testing done centrally *Note: leftover 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). The test will be performed for all participants who are seropositive. • 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)

	• Serum samples for humoral immunogenicity	• Non-Immuno Subset: on study visits 2, 3, 6, and the early exit visit (if applicable) • Immuno Subset: on study visits 2, 3, 4, 5, 6, 7, and 8, and the early exit visit (if applicable)
	• Serum sample for humoral immunogenicity and for sero-confirmation of SARS-CoV-2 infection	• On Day 1, COVID-19 Day 3-5 and COVID-19 Day 29
	• RNAseq blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity (PAXgene tubes, whole blood)	• On Day 1, COVID-19 Day 3-5, and COVID-19 Day 29

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, if applicable, 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 (or legally acceptable representative based on local regulations) 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.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally provide consent after the oral consent of the participant is obtained.

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 (or his or her legally acceptable representative based on local regulations) 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 biomarker and 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

A DSMB (also known as 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 1a (2,000 participants) and stage 2a (2,000 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.

The DSMB will also review 3-day safety data (consisting of all Grade 4 AEs and all SAEs [including those from the ongoing Phase 1/2 studies]) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

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 DSMB of any AE of concern.

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

In addition, the DSMB will formally monitor the infections in all groups to conclude both non-efficacy and efficacy. The DSMB 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 PSRT 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 DSMB; they are unblinded and provide the DSMB with the statistical analysis based on unblinded data. As the DSMB, 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 DSMB through secure communication procedures. At this point the DSMB 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

The Sponsor Committee responsibilities, authorities, procedures and their interactions with the DSMB will be documented in the DSMB 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 during monitoring visits and 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 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, 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 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.

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 verification. Remote source data verification 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 compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). 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 verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying 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, but 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[53], 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)
- Exposure to a sponsor study vaccine from breastfeeding

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 Woman of Childbearing Potential

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman 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 woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman 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					
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					
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 (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.

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						
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						
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 (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.

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 Form (MA-COV) Form

Section 1: To be completed in all healthcare settings (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:
Optional 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 (swab) taken:_

☐ **Mid-turbinate swab sample** ☐ **Saliva sample**

☐ **Sputum sample** ☐ **Other (specify):** _____

Specify results: _____

VITAL SIGNS

Temperature (ºC/ºF): _____

Respiratory rate: _____

Pulse: _____

Systolic and Diastolic Blood Pressure: _____

Oxygen saturation: _____

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
Did the patient experience any of these cardiovascular signs or symptoms? • **Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, SpO_2 ≤93% on room air at sea level[a], or PaO_2/FiO_2 <300 mmHg)** ☐ Yes ☐ No ▪ **Respiratory failure requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO** ☐ Yes ☐ No ▪ **Shock (systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm Hg or requiring vasopressors)** ☐ Yes ☐ No ▪ **Significant acute renal or hepatic dysfunction** ☐ Yes ☐ No ▪ **Radiologic evidence of DVT** ☐ Yes ☐ No
Did the patient experience any of these neurological signs or symptoms? ▪ **Symptoms or signs of stroke** ☐ Yes ☐ No ▪ **Numbness, tingling, or weakness face or limbs** ☐ Yes ☐ No

[a] SpO_2 criteria will be adjusted according to altitude

▪ **Difficulty speaking or forming speech**	□ **Yes** □ **No**
▪ **Difficulty understanding speech**	□ **Yes** □ **No**
▪ **Feelings of confusion**	□ **Yes** □ **No**
Did the patient experience any of these signs or symptoms?	
▪ **Cough**	□ **Yes** □ **No**
▪ **Sore throat**	□ **Yes** □ **No**
▪ **Malaise**	□ **Yes** □ **No**
▪ **Headache**	□ **Yes** □ **No**
▪ **Myalgia**	□ **Yes** □ **No**
▪ **Gastrointestinal symptoms**	□ **Yes** □ **No**
▪ **Chilblains/pernio (red or bruised looking feet or toes)**	□ **Yes** □ **No**
▪ **Anosmia (olfactory or taste disorders)**	□ **Yes** □ **No**

MANAGEMENT	
ANY TYPE OF MANAGEMENT OTHER THAN MEDICATION? *(including nebulizer treatments, IV fluids, intubation, mechanical ventilation, etc.)*	□ **Yes** □ **No**
If yes, please specify: _____	

Section 2: COVID-19-related Procedures completed during the event.

SUPPLEMENTAL OXYGEN	
Was supplemental oxygen administered? *If 'yes' selected, please fill out remaining questions in this section.*	□ **Yes** □ **No**
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:	

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: Protocol Amendment History

This is an original protocol.

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INVESTIGATOR AGREEMENT

VAC31518 (JNJ-78436735) Clinical Protocol VAC31518COV3001

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 intervention, 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: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Jerald Sadoff, MD

Institution: Janssen Vaccines & Prevention B.V.

Signature: Jerald Sadoff Digitally signed by Jerald Sadoff DN: cn=Jerald Sadoff, o=Janssen Infectious Diseases and Vaccines, ou, PPD c=US Reason: I am approving this document. Date: 2020.07.22 16:32:52 -04'00' Adobe Reader version: 11.0.20 Date: _____
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 142
Status: Approved, Date: 22 July 2020

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

Protocol VAC31518COV3001; 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

Status: Approved
Date: 14 December 2020
EDMS number: EDMS-RIM-50860, 6.0

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

Confidentiality Statement

The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	This document
Amendment 2	29 October 2020
Amendment 1	15 September 2020
Original Protocol	22 July 2020

Amendment 3 (This document)

Overall Rationale for the Amendment: The main purpose of this amendment is to add first occurrence of molecularly confirmed, moderate to severe/critical COVID-19, with onset at least 28 days post-vaccination as a co-primary endpoint in addition to the current primary endpoint counting as of 14 days post-vaccination. The applicable secondary and exploratory endpoints were updated similarly to also include COVID-19 cases with onset at least 28 days post-vaccination. In addition, the total sample size was reduced from 60,000 to approximately 40,000 participants. The protocol is further amended to change the conditions for monitoring whether efficacy greater than 30% is achieved using the sequential monitoring algorithm: (1) The minimum number of COVID-19 cases meeting the primary case definition needed to start the efficacy monitoring was modified to at least 42 instead of 20, (2) The need for a follow-up of 8 weeks for 50% of the participants prior to an initial look at an efficacy signal if the other conditions are met was removed.

These and other changes made to the clinical protocol of study VAC31518COV3001 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 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 8.1.3.1 Case Definition for Moderate to Severe/Critical COVID-19 8.1.3.6 Clinical Severity Adjudication Committee 9.1 Statistical Hypotheses 9.2.1 Efficacy (Total Sample Size) 9.5.1 Primary Endpoints Evaluation 9.5.1.1 Study Monitoring 9.5.2 Secondary Endpoints 9.8 Interim Analysis and Committees 10.3.6 Committees Structure	A co-primary endpoint was added counting COVID-19 cases from 28 days post-vaccination (Day 29), in addition to from 14 days post-vaccination (Day 15). The applicable secondary and exploratory endpoints were updated to also include COVID-19 cases with onset at least 28 days post-vaccination, in addition to from 14 days post-vaccination.	This change will allow for formal testing and reporting of the primary endpoint counting cases from 28 days post-vaccination as an additional condition for success along with the 14 days post-vaccination endpoint results. Maintaining the original primary endpoint will preserve trial integrity. This approach will allow to provide the most accurate description of the vaccine efficacy and to assess vaccine efficacy as early as 14 days post-vaccination.
3 OBJECTIVES AND ENDPOINTS	Deletion of the exploratory endpoint relating to evaluation of the occurrence, severity and duration of COVID-19 episodes in participants who received Ad26.COV2.S, as compared to placebo, by the Clinical Severity	The Clinical Severity Adjudication Committee only exists to determine severe/critical cases of COVID-19.

Section Number and Name	Description of Change	Brief Rationale
	Adjudication Committee, previously known as the Clinical Evaluation Committee.	
9.2.1 Efficacy (Total Sample Size) 9.2.4 Safety (Safety Subset)	The total sample size was reduced from 60,000 to approximately 40,000. The paragraph on the operational futility was removed.	The incidence of moderate to severe COVID-19 seen in the US and reported in other COVID-19 vaccine studies is significantly higher than assumed at the time of protocol planning. Furthermore, based on that incidence and modeling, there is a high degree of probability that an efficacy signal meeting the prespecified criteria in this amendment will be reached at, or prior to, the time when 50% of participants will have been followed for 8 weeks from the time of vaccination.
1.1 Synopsis 9.5.1 Primary Endpoints Evaluation	The conditions for monitoring whether efficacy greater than 30% is achieved using the sequential monitoring algorithm were changed: (1) The minimum number of COVID-19 cases with onset at least 28 days after vaccination meeting the primary case definition needed to start the efficacy monitoring was modified to at least 42 instead of 20. (2) The need for a follow-up of 8 weeks for 50% of participants prior to an initial look at an efficacy signal if the other conditions are met, was removed. In addition, text was added to clarify the timing of primary and interim analyses.	(1) The minimum number of COVID-19 cases was increased to have a more robust signal at the time of the efficacy declaration. (2) This change was made to expedite submissions to ensure the vaccine is made available to the public as soon as possible. Following 50% of participants for 8 weeks from the day of vaccination meets the sponsor's understanding of the requirement for 8 weeks median follow-up for a 40,000-participant study.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 9.5.2 Secondary Endpoints	A secondary objective and endpoint were added assessing the efficacy of the vaccine in the prevention of molecularly confirmed, severe/critical COVID-19 with onset at least 14 days post-vaccination and 28 days post-vaccination.	With the increased incidence of disease that is being observed, the likelihood of having enough severe cases of COVID-19 to examine vaccine efficacy against this endpoint has increased. Vaccine efficacy against severe disease is considered an important endpoint for a 1-dose vaccine.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 All Participants 3 OBJECTIVES AND ENDPOINTS 8.1.3 Efficacy Assessments 8.1.3.5 SARS-CoV-2 Seroconversion Assessment 8.1.4 Immunogenicity Assessments 10.2 Appendix 2: Clinical Laboratory Tests	An exploratory objective and endpoint were added assessing the effect of the vaccine on confirmed asymptomatic or undetected infections by testing serologic conversion between baseline and 28 days post-vaccination.	This change allows the evaluation of the effect of the vaccine on asymptomatic infections up to Day 29, in line with other efficacy endpoints.
3 OBJECTIVES AND ENDPOINTS	An exploratory objective and endpoint to examine the degree of frailty were added.	The vaccine will be especially useful in the elderly population with co-morbidities. The frailty index has been utilized as a tool to summarize the degree of frailty that a participant has.
1.1 Synopsis 2.3.1 Risks Related to Study Participation 3 OBJECTIVES AND ENDPOINTS 8.1.3 Efficacy Assessments 8.1.3.6 Clinical Severity Adjudication Committee 10.3.6 Committees Structure	The Clinical Evaluation Committee was replaced by the Clinical Severity Adjudication Committee.	The standard case definition of severe/critical disease may not cover all situations where clinical judgement would disagree with the classification on clinical grounds.
1.1 Synopsis 8.1.3.1 Case Definition for Moderate to Severe/Critical COVID-19	Addition of text defining the definitive role of the Clinical Severity Adjudication Committee in determining whether cases are severe/critical cases of COVID-19.	Clarification of the definitive role of the Clinical Severity Adjudication Committee in defining the severity of cases of COVID-19.
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 8.8 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 United States (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 3 OBJECTIVES AND ENDPOINTS 8.1.4 Immunogenicity Assessments	psVNA was removed from the protocol.	Due to lack of sensitivity of the evaluated psVNA, the assay has been removed from the protocol

Section Number and Name	Description of Change	Brief Rationale
	wtVNA will be used to support the exploratory immunogenicity endpoint.	wtVNA is currently only qualified and not validated and can therefore not be used to support a secondary immunogenicity endpoint unless validated.
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	Further clarifications are made to the procedures to be followed in case of (suspected) COVID-19.	Alignment across the protocol and clarifications on the procedures to be followed in case of (suspected) COVID-19.
5.1 Inclusion Criteria	Inclusion criterion 4 was updated to clarify that all comorbidities need to be stable and well-controlled, those that are associated with severe COVID-19 AND those that are not associated with severe COVID-19. In addition, a time frame was added for criteria a and b for stable/well-controlled HIV infection.	Clarification
5.1 Inclusion Criteria	In inclusion criterion 4, 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
5.1 Inclusion Criteria	It was clarified in inclusion criterion 9 that participants with visual impairment are eligible and may have caregiver assistance in completing the eCOA questionnaires.	Clarification
5.2 Exclusion Criteria	In exclusion criterion 3, “Patients 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	In exclusion criterion 4, it was clarified that autologous blood transfusions are not excluded.	Clarification
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 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine After the End of the Study 9.7 Safety Analysis	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.

Section Number and Name	Description of Change	Brief Rationale
10.8 Appendix 8: Medically-attended COVID-19 (MA-COV) Form	The MA-COV form has been updated to also capture hyperinflammatory syndrome.	To ensure collection of all necessary information in order to determine the severity of COVID-19 per the case definitions and clarification purposes.
2.3.1 Risks Related to Study Participation 5.1 Inclusion Criteria	It was clarified that the use of condoms is not considered an acceptable contraceptive barrier method due to the failure rate of female and male condoms.	Clarification
8 STUDY ASSESSMENTS AND PROCEDURES	It was clarified that in case of home visits, assessments that cannot be delegated to a designee must be performed by an appropriate site staff member via a phone call or telemedicine.	Clarification
8.7 Risk Factor Assessment 9.4 Participant Information	It was 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
6.3 Measures to Minimize Bias: Randomization and Blinding 9.5.1 Primary Endpoints Evaluation	The timepoints of analyses at which the sponsor will be unblinded were clarified.	Clarification
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Addition of minor clarifications. Alignment across sections in the protocol.

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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

This study is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V) in collaboration with Operation Warp Speed (OWS), which also encompasses the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the COVID-19 Prevention Trials Network (COVPN).

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
Co-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 post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
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], severe/critical COVID-19[b], as compared to placebo	• First occurrence of molecularly confirmed[a], severe/critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], severe/critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
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 post-vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)

Objectives	Endpoints
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, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	• First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, 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 post-vaccination (Day 15) • First occurrence of COVID-19 requiring medical intervention and linked to any molecularly confirmed[a], COVID-19[b,c] at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe/critical COVID-19[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
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 post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], mild COVID-19[c], at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition[d]	• First occurrence of molecularly confirmed[a] COVID-19[d] at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a] COVID-19[d] at least 28 days post-vaccination (Day 29)
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[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 post-vaccination (Day 15). • 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 28 days post-vaccination (Day 29).

Objectives	Endpoints
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 28 days after vaccination (Day 29)
Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination, and in terms of unsolicited AEs during 28 days post-vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during the 7 days following vaccination and of unsolicited AEs during the 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA

[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 co-primary hypotheses of vaccine efficacy (VE) in the PP population. For both co-primary endpoints, the following hypothesis will be tested:

H0: VE ≤30% versus H1: VE >30% and each hypothesis will be evaluated at a 2.5% one-sided significance level.

The co-primary endpoints 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 vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition, with onset at least 28 days after vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

If testing for both primary endpoint hypotheses 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% one-sided significance level.

Case Definitions

All potential severe/critical COVID-19 cases defined as those cases that meet the severe/critical definition by scoring of signs and/or symptoms or meet the moderate endpoint definition with a total of 3 or more signs and/or symptoms will be assessed independently by a Clinical Severity Adjudication Committee. This committee will independently evaluate the severity of the COVID-19 cases in a blinded manner. Classification of the severe/critical designation in terms of severity will be based on the highest degree of severity during the observation period. Since this committee will evaluate case severity in a blinded manner it will be able to objectively evaluate moderate vs severe cases which will be its main priority.

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 co-primary endpoints (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]:

[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).

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

All cases meeting the severe/critical criteria will be adjudicated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

All cases meeting the moderate case definition and that include ≥3 signs and/or symptoms from the list of signs and symptoms will be evaluated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive.

Case Definition for Mild COVID-19

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

  AND at any time during the course of observation[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.

[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).

OVERALL DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 to <60 years of age and ≥60 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 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 is safe. The sponsor has therefore decided to proceed with the single dose regimen at a 5×10^{10} virus particles (vp) dose level in this Phase 3 study.

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.

Table: Vaccination Schedule VAC31518COV3001

Group	N	Day 1
1	20,000	Ad26.COV2.S (5×10^{10} vp)
2	20,000	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.

The following enrollment strategy will be used:

- Stage 1a: Initially, approximately 2,000 participants ≥18 to <60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients) will be enrolled, based on acceptable Day 29 safety and acceptable immunogenicity data, including T-helper 1/T-helper 2 (Th1/Th2), from the corresponding age group (Cohort 1a) of the first-in-human (FIH) study VAC31518COV1001.
- Stage 1b: After a vaccination pause (in the age group ≥18 to <60 years of age) to allow the Data Safety Monitoring Board (DSMB, also known as an Independent Data Monitoring Committee [IDMC]) to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies), if no safety concerns are identified enrollment will proceed, expanding enrollment to include ≥18- to <60-year-old participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19.

In Stage 1a and 1b combined, the enrollment of participants aged ≥18 to <40 years will be limited to approximately 20% of the total study population.

- Stage 2a: Initially, approximately 2,000 participants ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients). Considering the data from study VAC31518COV1001 (including data on elderly), Stage 2a will run in parallel with Stage 1a, unless this is not allowed per local Health Authority guidance.
- Stage 2b: After a vaccination pause (in the age group ≥60 years of age) to allow the DSMB to examine Day 3 safety data (ie, from Day 1 to Day 3;including safety data from Stage 1 and the ongoing clinical studies) from Stage 2a, if no safety concerns are identified in this population enrollment will proceed, expanding enrollment to include ≥60 year-old participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19.

Stage 2 will enroll a minimum of approximately 30% of the total study population.

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.

The duration of individual participation, including screening, will be maximum 2 years and 1 month. 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 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. Biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity will also be studied. 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. 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. 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. The statistical analyses will be described in detail in a statistical analysis plan.

Until 1-year post-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 post-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 vaccination, ie, until the last study visit. Every effort will be made to

[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 no pregnant women are allowed to participate in the study.

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.

Any positive RT-PCR test result regardless if it is obtained outside the study or at a study visit will be considered a trigger to start COVID-19 procedures. All participants with COVID-19-like signs or symptoms meeting the prespecified criteria for suspected COVID-19[a] and all participants with at least 1 positive RT-PCR test for SARS-CoV-2 on COVID-19 Day 1-2 or 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 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 will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

A DSMB will be commissioned for this study.

NUMBER OF PARTICIPANTS

Overall, a target of approximately 40,000 adult participants (≥18- to <60-year-old and ≥60-year-old, with and without relevant comorbidities) will be randomly assigned in this study. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender.

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.

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

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

- Placebo: 0.9% sodium chloride (NaCl) solution

For blinding purposes, all participants will receive Ad26.COV2.S or placebo at Day 1, 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.

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 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination.

IMMUNOGENICITY EVALUATIONS

Blood will be collected from all non-Immunogenicity Subset participants for humoral immunogenicity assessments at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after 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 at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year, 18 months, and 2 years after 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 Day 1-2 or Day 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.

[a] World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID-19 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.

Table: Immunogenicity and Transcriptomic 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
Transcriptomic Assay	**Purpose**
Supportive of Exploratory Objectives	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in unstimulated cells or whole blood

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; RNA = ribonucleic acid; 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 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after 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 2,000 participants in each of the 2 age groups will remain under observation at the study site for at least 30 minutes post-vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 2,000 participants no acute reactions have been observed in the age groups, the observation period at the study site may be reduced to at least 15 minutes post-vaccination for the remaining participants in the study.

[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).

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 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 (regardless of the causal relationship) are to be reported from the moment of 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 vaccination until 6 months after the 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 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 vaccination until 7 days post-vaccination.
- All other unsolicited AEs, whether serious or non-serious, will be recorded from the time of vaccination until 28 days post-vaccination.

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 60%.
- 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 for the co-primary endpoints 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 vaccination (Day 15) and at least 28 days after vaccination (Day 29) with study vaccine.

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 154, based on events in each active vaccination and placebo group, according to the primary endpoints case definition of moderate to severe/critical COVID-19.

If the primary hypotheses 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%.

Further details on the sample size calculation are provided in the body of the protocol.

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 a 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:** Participants in the FAS who receive study vaccine and who are seronegative at the time of vaccination 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:** All randomized and vaccinated participants, 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 unblinding.

Efficacy Analyses

The study will have the following timepoints for efficacy analyses:

1. The evaluation of the primary objective will be performed as soon as the TNE has been reached for both co-primary endpoints, or earlier based on sequential monitoring of both co-primary endpoints. Sponsor unblinding will occur but investigator and participants remain blinded until study completion (end-of-study analysis). The unblinding strategy of the sponsor will be described in a separate document.
2. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached (8-week median follow-up timepoint). If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.
3. After the primary analysis, additional analyses to support health authority interactions will be planned, as deemed appropriate.
4. The final analysis will be performed when the last participant completes the visit 12 months post-vaccination or discontinues earlier.
5. The end-of-study analysis will be performed when all participants have completed the visit 24 months post-vaccination or discontinued earlier.

Primary Endpoints

The study is designed to test the co-primary hypotheses of VE in the PP population. For both co-primary endpoints, the following hypothesis will be tested: H0: VE ≤30% versus H1: VE >30%. The co-primary endpoints 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 vaccination (Day 15) and with onset at least 28 days after vaccination (Day 29) with Ad26.COV2.S versus placebo, separately, 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.

Evaluation of the Primary Endpoints

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=60% 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:

1. Establishing the hypothesis H1: VE>30% for each co-primary endpoint

AND

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

To evaluate the primary null hypotheses: H0: VE ≤30% versus H1: VE >30% for the co-primary endpoints, the truncated sequential probability ratio test will be used based on accumulating event data for each co-primary endpoint. 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=60% using a one-sided alpha=0.025 against H0:VE≤30%. For the evaluation of the favorable ratio against the severe/critical COVID-19 endpoints a sequential boundary corresponding to a VE point estimate ≥50% and a minimum of 5 events in the placebo group will be prespecified. 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 with onset at least 28 days after vaccination
2. At least 42 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 with onset at least 28 days after vaccination.
3. A subset of at least 5 cases meeting the primary endpoint definition of severe/critical COVID-19 with onset at least 28 days after vaccination.

No interim evaluation will be done, until those conditions are fulfilled. Monitoring for efficacy will not start before the above conditions 1-3 are met and will occur at least once a week by the SSG of the DSMB until the prespecified boundaries have been crossed.

The efficacy analysis will be triggered by either:

1. a) An interim evaluation if all prespecified efficacy boundaries have been met OR if 154 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 are observed for events with onset at least 28 days after vaccination.

   AND

   b) The above 3 conditions are met.

OR, alternatively,

2. If the prespecified non-efficacy boundary has been met (evaluating events with start 28 days after 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.
3. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached (8-week median follow-up timepoint), an additional analysis will be performed when that follow-up timepoint is reached. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

If more than 154 primary endpoints are observed for events with onset at least 28 days after vaccination before the 3 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 boundaries and above criteria are met, the SSG will inform the DSMB and if deemed appropriate by the DSMB, a meeting with the DSMB and Oversight Group will be set up to discuss the efficacy signal. Upon this meeting the sponsor representative on the Oversight Group can trigger internal decision procedures to initiate health authority interactions based on the outcome of the study.

The primary efficacy analysis will pool data across populations (both age groups with and without comorbidities) to evaluate the primary and secondary objectives. In addition, these will be supplemented with a subgroup analysis for age group (18 to <60 years, ≥60 years) and comorbidities employing a descriptive summary, including 95% confidence intervals to describe the VE in each subpopulation. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (≥70 years, ≥80 years).

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 a DSMB (also known as an IDMC). In general, the DSMB will monitor safety data on a regular basis to ensure the continuing safety of the participants. The DSMB will review unblinded data.

The DSMB will review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews. Enrollment will not be paused during other safety reviews. The DSMB responsibilities, authorities, and procedures will be documented in the DSMB 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 efficacy analysis is triggered. If the stopping boundary is met, then the SSG immediately informs the Chair of the DSMB through secure communication procedures. At this point the DSMB will convene and provide a recommendation to the Oversight Group, which includes a sponsor representative as a core member. 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 DSMB will formally monitor the SARS-CoV-2 events to conclude both non-efficacy and efficacy. The DSMB will evaluate in an unblinded fashion whether superiority is established for the co-primary endpoints 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 endpoints 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 DSMB will contain unblinded events and a report provided to the sponsor will contain blinded events. While it is the primary responsibility of the sponsor to make decisions regarding study operations and modifications based on monitoring of study vaccine-blinded primary events from the study, the DSMB can evaluate the progress towards primary endpoints targets in the context of the study vaccine-unblinded data, and based on this review may recommend to the Oversight Group, which includes a sponsor representative as a core member, 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 DSMB charter, with the statistical details in the SAP.

The SAP will describe the planned analyses in greater detail.

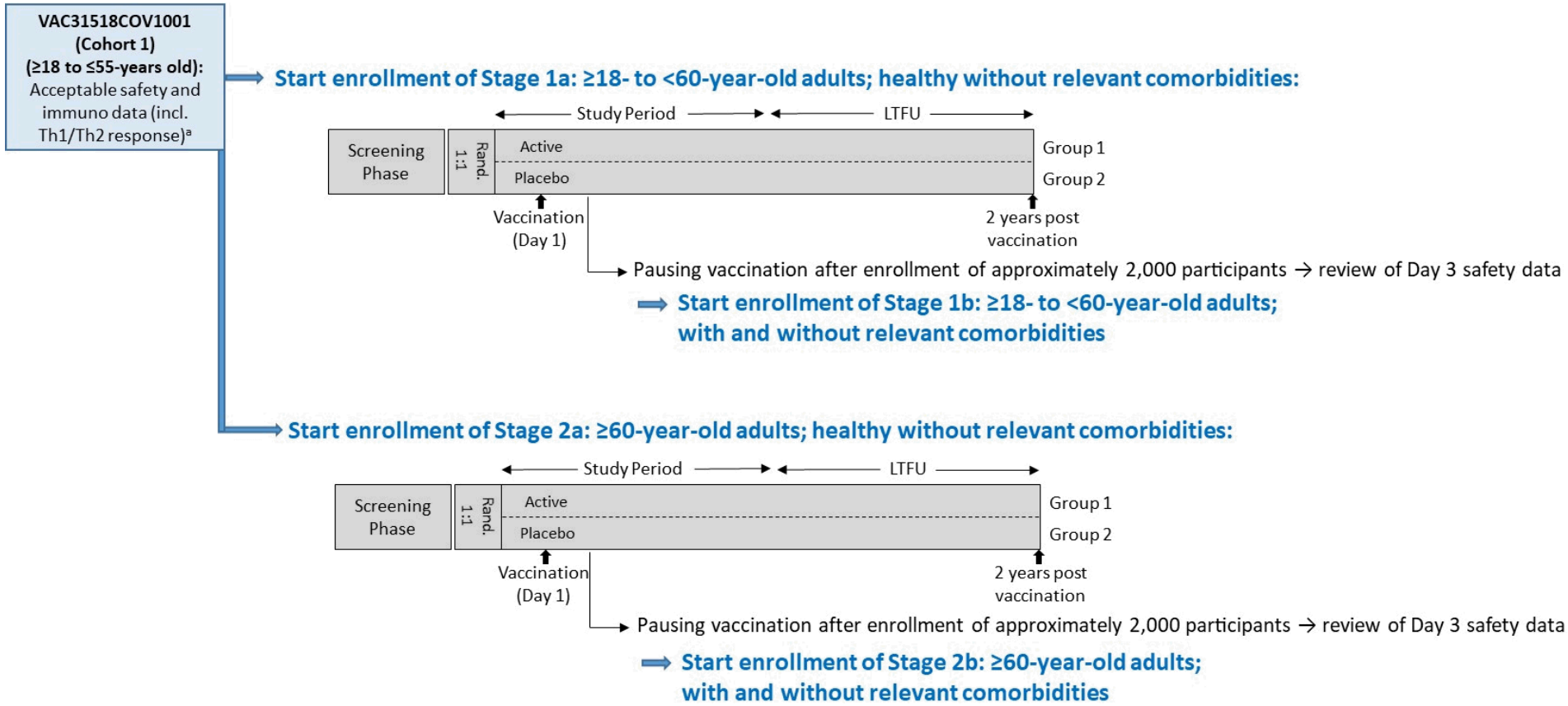
Unblinding due to availability of an authorized/licensed COVID-19 vaccine

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 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. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the schedule 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 VAC31518COV3001



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

[a] At the time of protocol Amendment 1 writing, immunogenicity and safety data from Cohort 1a (≥18-≤55 years of age) and Cohort 3 (≥65 years of age) 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 and that the dose is considered safe. Stage 2a can therefore be enrolled in parallel to Stage 1a, unless this is not allowed per local Health Authority guidance.

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

In Stage 1a and 1b combined, the enrollment of participants aged ≥18 to <40 years will be limited to approximately 20% of the total study population. Stage 2, including participants aged ≥60 years, will enroll a minimum of approximately 30% of the total study population. 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 VAC31518COV3001 based on data from study VAC31518COV1001.
Refer to Section 2.2 for details about the VAC31518COV1001 study.
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	7	8	Exit[c]
Visit Timing		Vac	Vac + 28 d	Vac + 70 d	Vac + 24 w	Vac +52 w	Vac +78 w	Vac +104 w	
Visit Day/Week	Day -28 to 1	Day 1	Day 29	Day 71	Month 6 (Week 24)	Year 1 (Week 52)	Month 18 (Week 78)	Year 2 (Week 104)	
Visit Window			±3 d	±3 d	±21 d	±21 d	±28 d	±28 d	
Visit Type	Screening	Vaccination	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Early Exit
Informed consent[d]	●								
Inclusion/exclusion criteria	●	●[#,e]							
Demographics	●								
Risk factor assessment[f]		●[#]		●	●	●			
Optional consent to access medical data			●[g]						
Relevant medical history[h]/prestudy therapies[i]	●	●[#]							
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]		●[#]							
Biomarker RNAseq blood sample (PAXgene tubes, whole blood), mL[o]		●[#]2.5	●2.5						
Blood sample collection for screening serological test for anti-SARS-CoV-2 antibody	●[p]								
MRU questionnaire (baseline version)[q]		●[#]							
Pre-vaccination symptoms[r]		●[#]							
eCOA training and set-up[s]		●[#]							
Distribution of thermometer		●[#]							
Distribution of pulse oximeter[t]		●[#]							
Distribution of MA-COV form[u]		●[#]							
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**	**7**	**8**	**Exit[c]**
Visit Timing		**Vac**	**Vac + 28 d**	**Vac + 70 d**	**Vac + 24 w**	**Vac +52 w**	**Vac +78 w**	**Vac +104 w**	
Visit Day/Week	**Day -28 to 1**	**Day 1**	**Day 29**	**Day 71**	**Month 6 (Week 24)**	**Year 1 (Week 52)**	**Month 18 (Week 78)**	**Year 2 (Week 104)**	
Visit Window			**±3 d**	**±3 d**	**±21 d**	**±21 d**	**±28 d**	**±28 d**	
Visit Type	**Screening**	**Vaccination**	**Safety and Immuno**	**Safety and Immuno**	**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)[v]		●[#]							
Vaccination		●							
Post-vaccination observation[w]		●							
(Suspected) COVID-19 surveillance (symptom check)[x]		*Continuous*							
MAAE recording[y]		*Continuous*							
(S)AE recording[z]		*Continuous*							●
Concomitant therapies[aa]		*Continuous*							●
Humoral immunogenicity (serum), mL (non-Immunogenicity Subset Participants)[bb]		●[#]10	●10	●10	●10	●10			●[cc]10
IMMUNOGENICITY SUBSET ONLY									
Humoral immunogenicity (serum), mL[dd]		●[#]15	●15	●15	●15	●15	●15	●15	●[cc]15
SAFETY SUBSET ONLY									
Solicited AE recording[ee]		*Cont +7d*							●[l]
Unsolicited AE recording[ff]		*Cont +28 d*							●[gg]
Ruler training and distribution of ruler[hh]		●							
Participant e-Diary review			●						
Approx. blood draw per visit, mL: 400 participants (Immunogenicity Subset) [Other participants]		17.5 [12.5]	17.5 [12.5]	15 [10.0]	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]		17.5 [12.5]	35.0 [25.0]	50.0 [35.0]	65.0 [45.0]	80.0 [55.0]	95.0 [55.0]	110.0 [55.0]	

[#] pre-vaccination

a. Screening will be performed within 28 days prior to the 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. For those participants who are unable to continue participation in the study up to Visit 8, 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).
d. 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.
e. Check clinical status again before study vaccination.
f. 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 analysis.
g. 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 8.8). 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 (see Section 4.2.1).
h. 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 medical conditions 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.
i. 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 vaccination must be recorded at screening.
j. 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. Blood pressure is to be graded by the investigator using the toxicity grading scale in Appendix 9.
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. Blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity.
p. 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.
q. MRU over the last 3 months before vaccination will be collected by interview with the participant and recorded in the eCRF.
r. 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.
s. 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.

t. 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).
u. The Medically-attended -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.
v. 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.
w. The first 2,000 participants in each of the 2 age groups will be closely observed for at least 30 minutes post-vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 2,000 participants no acute reactions have been observed in the age groups, the remaining participants in the study will be closely observed for at least 15 minutes post-vaccination. 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.
x. Until 1-year post-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 post-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.
y. MAAEs are to be reported for all participants from the moment of vaccination until 6 months after the 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.
z. 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 (regardless of the causal relationship) are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. Special reporting situations, whether serious or non-serious, are to be recorded 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.
aa. Refer to Section 6.8 for collection and recording of concomitant therapies associated with SAEs, solicited and unsolicited AEs, and MAAEs.
bb. Blood sample for humoral immunity at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination also includes sample for sero-confirmation of SARS-CoV-2 infection.
cc. Blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw.
dd. Blood sample for humoral immunity at Day 1 (pre-vaccination), Day 71, 6 months, and 1 year after vaccination also includes sample for sero-confirmation of SARS-CoV-2 infection. Samples will be collected for 400 participants at selected sites.

ee. 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 vaccination until 7 days post-vaccination.
ff. All other unsolicited AEs will be reported for the vaccination from the time of vaccination until 28 days post-vaccination. In order to perform the safety assessment after 2,000 participants have been vaccinated in Stages 1a and 2a, 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.
gg. If within 28 days of the vaccination.
hh. 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[b,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]
Biomarker RNAseq blood sample (PAXgene tubes, whole blood), mL[r]			●2.5			●2.5
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[s] (ePROs to be completed by the participant in the eCOA)	- - - - - - - - - - - - - - - - - - *Daily* - - - - - - - - - - - - - - -					●[t]
In case of no signs or symptoms: (Suspected) COVID-19 surveillance (symptom check)	- - - - - - - - - - - - - - *At least twice a week* - - - - - - - - - -					●
Risk factor assessment[u]			●			
Vital signs[v]		●				●
Targeted physical examination		●				●
Pulse oximetry by site staff		●				●
Pulse oximetry by the participant (ePRO to be completed by the participant in the eCOA)[w]	●[n]	- - - - - - - - - *3 times a day* - - - - - - - - -				
Medical history (including recent flu or pneumococcal vaccination) and description of COVID-19 episode (collected by interview with the participant)			●			●
MRU questionnaire (collected by interview with the participant)[x]			●			●
Capture medical information from medical visits for COVID-19 or COVID-19 complications (MA-COV form)[y]	- *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 meet the prespecified criteria for suspected COVID-19 (Section 8.1.1) on COVID-19 Day 1-2 and COVID-19 Day 3-5 or who have a positive test result for SARS-CoV-2 on COVID-19 Days 1-2 or 3-5 visits.

c. Participants should be encouraged by the site to collect nasal swabs and saliva samples as indicated in the Schedule 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 Schedule 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 and/or institutional 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). 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. 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).
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.
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. Blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity.

s. 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.
t. If the participant does not have symptoms at that time, he/she will only need to complete the (suspected) COVID-19 surveillance (symptom check).
u. 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.
v. 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.
w. 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.
x. Data collected as part of the MRU will be recorded in the eCRF.
y. 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 Schedule 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 July 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".

Study VAC31518COV3001 is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V) in collaboration with Operation Warp Speed (OWS), which also encompasses the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the COVID-19 Prevention Trials Network (COVPN).

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.[17,70] 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.[40,42,71] 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 initial effort will be to rapidly demonstrate safety and immunogenicity in adults aged ≤55 years in study VAC31518COV1001, in order to initiate the efficacy study VAC31518COV3001 in this age group as soon as possible, and to evaluate safety and immunogenicity in older adults aged ≥65 years. 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.[73]

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

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[20,66] 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.[42,66] 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.[63,64] 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.[10,61]

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.[65] 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.[73] 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.[15,73] 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.[15,65] 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[8,53,69,72] and the only viral protein that can elicit protective immunity in animal models.[5,6,9,52,67] Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen.

At the time of protocol Amendment 1 writing, initial immunogenicity and safety data (28 days post-Dose 1 data from Cohort 1a and available data from Cohort 3) 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 is safe. These data support the sponsor's decision to proceed with the single dose regimen at a 5×10^{10} vp dose level in this Phase 3 study.

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.[2,4,19,45,48,49,51,60,62,68] This type 1 polarity of the immune response is thought to minimize the risk of enhanced disease after SARS-CoV-2 infection.

Study VAC31518COV3001 will include ≥18- to <60-year-old participants and participants ≥60 years of age.

Study VAC31518COV3001 will start with enrollment in Stage 1 (≥18- to <60-year-old participants) based on all available safety and reactogenicity data, and all relevant and available immunogenicity data from Cohort 1a (adults ≥18 to ≤55 years) of the first-in-human (FIH) study with the vaccine candidate (Ad26.COV2.S; study VAC31518COV1001; see Section 2.2), immunogenicity data (including Th1 responses) from non-human primates (NHPs), and efficacy in hamsters and NHPs and all other relevant data. Immunogenicity data from Cohort 1a of study VAC31518COV1001 will include virus neutralization assay (VNA), enzyme-linked immunosorbent assay (ELISA) and Th1/Th2 response data.

Because the data from study VAC31518COV1001 (including data on elderly) demonstrated that Ad26.COV2.S at 5×10^{10} vp is both immunogenic and safe, Stage 2a (participants ≥60 years of age) of study VAC31518COV3001 will start enrolling in parallel to Stage 1a, unless this is not allowed per local Health Authority guidance.

Within Stage 1a and Stage 2a, enrollment will be restricted to participants without comorbidities that are associated with increased risk of progression to severe COVID-19 as described below.

The study will start by enrolling approximately 2,000 participants (≥18- to <60-year-old) without comorbidities that are associated with increased risk of progression to severe COVID-19 (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients) (Stage 1a of the study), then vaccination will be paused to allow the Data Safety Monitoring Board (DSMB) to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies). If no safety concerns are identified, enrollment will proceed, expanding enrollment to ≥18- to <60-year-old participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 1b) (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).

In parallel to Stage 1a, in Stage 2 of the study, approximately 2,000 adults ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (Stage 2a; including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients). Following enrollment of these initial 2,000 participants in Stage 2a, further vaccination in Stage 2 of the study will be paused to allow the DSMB to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from Stage 1 and the ongoing clinical studies). Upon confirmation that there are no safety concerns in this population or in the Stage 1 population up to that point, enrollment will proceed, including participants aged ≥60 years with and without comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 2b) (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 (including ≥18- to <60-year-old and ≥60-year-old participants, and participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19) will be approximately 40,000 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.

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

The FIH study VAC31518COV1001 will be ongoing at the time of initiation of study VAC31518COV3001. 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 1). 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.

The study includes the following cohorts (Table 1):

1. Cohort 1:
   a. Cohort 1a: 375 participants (75 participants per group) aged ≥18 to ≤55 years who will be randomized in parallel in a 1:1:1:1:1 ratio to 1 of 5 vaccination groups.
   b. Cohort 1b: 25 participants (5 participants per group) aged ≥18 to ≤55 years who will be enrolled at the Beth Israel Deaconess Medical Center (BIDMC) and randomized in parallel in a 1:1:1:1:1 ratio to 1 of 5 vaccination groups. Additional exploratory immunogenicity evaluations (eg, epitope mapping, passive transfer, and certain analyses of functional and molecular antibody characteristics) will be performed for Cohort 1b.
2. Cohort 2: 270 participants aged ≥18 to ≤55 years will be randomized to receive Ad26.COV2.S (240 participants) or a placebo (30 participants) in the primary regimen. Cohort 2 will include an evaluation of a single booster vaccination.
3. Cohort 3: 375 participants (75 participants per group) aged ≥65 years who will be randomized in parallel in a 1:1:1:1:1 ratio to 1 of 5 vaccination groups.

Table 1: Vaccination Schedules of Study VAC31518COV1001

Cohort 1a (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	75	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
2	75	Ad26.COV2.S 5×10^{10} vp	Placebo
3	75	Ad26.COV2.S 1×10^{11} vp	Ad26.COV2.S 1×10^{11} vp
4	75	Ad26.COV2.S 1×10^{11} vp	Placebo
5	75	Placebo	Placebo
Cohort 1b (Adults ≥18 to ≤55 years) [a]			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	5	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
2	5	Ad26.COV2.S 5×10^{10} vp	Placebo
3	5	Ad26.COV2.S 1×10^{11} vp	Ad26.COV2.S 1×10^{11} vp
4	5	Ad26.COV2.S 1×10^{11} vp	Placebo
5	5	Placebo	Placebo
Cohort 2a (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)** [b]	**Day 57** [b]
1-4	120	Ad26.COV2.S 5×10^{10} vp[c]	No vaccination
5	15	Placebo	No vaccination
Cohort 2b (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)** [b]	**Day 57 (Vaccination 2)** [b]
1-4	120	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
5	15	Placebo	Placebo
Cohort 3 (Adults ≥65 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	75	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp
2	75	Ad26.COV2.S 5×10^{10} vp	Placebo
3	75	Ad26.COV2.S 1×10^{11} vp	Ad26.COV2.S 1×10^{11} vp
4	75	Ad26.COV2.S 1×10^{11} vp	Placebo
5	75	Placebo	Placebo
Total	**1,045**		

a. Cohort 1b comprises 5 participants in each group who will be enrolled at Beth Israel Deaconess Medical Center (BIDMC) and for whom additional exploratory immunogenicity analyses will be performed.
b. Study vaccine will be administered as a single-dose (Day 1) or 2-dose (Day 1 and Day 57) primary regimen. Cohort 2 will also include an evaluation of a single booster vaccination at 6, 12, or 24 months after completion of the primary single-dose or 2-dose primary regimen.
c. Revised per VAC31518COV1001 Protocol Amendment 6, dated 19 September 2020.
N = number of participants; vp = virus particles.

At the time of protocol Amendment 1 writing, 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 is safe. The sponsor has therefore decided to proceed with the single dose regimen at a 5×10^{10} vp dose level in this Phase 3 study.

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 reminiscent of 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 VAC31518COV3001 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).

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 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 2,000 participants in each of the 2 age groups will remain under observation at the study site for at least 30 minutes after vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 2,000 participants no acute reactions have been observed in the age groups, the observation period at the study site may be reduced to at least 15 minutes 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 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 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). 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. The subset of cases with potential for severe disease will be assessed by the Clinical Severity Adjudication Committee (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 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 DSMB 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 DSMB 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 2,000 participants in each of the 2 age groups will remain under observation at the study site for at least 30 minutes after vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 2,000 participants no acute reactions have been observed in the age groups, the observation period at the study site may be reduced to at least 15 minutes 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.
- A DSMB 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 DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter. The DSMB will also review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stages 1a and Stage 2a, before enrollment of participants in Stages 1b and Stage 2b, respectively. 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 the following enrollment strategy to mitigate the risks for participants at increased risk of progression to severe COVID-19:
    - In Stage 1, the study will enroll ≥18- to <60-year-old participants (Stage 1 of the study) based on immunogenicity and safety data from Cohort 1a of study VAC31518COV1001 (see details in Section 2.1). In Stage 1a, approximately 2,000 participants without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients), then vaccination will be paused to allow the DSMB to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies). If no safety concerns are identified, enrollment will proceed, including ≥18- to <60-year-old participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 1b) (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).
    - In Stage 2 of the study, approximately 2,000 adults ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (Stage 2a; including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients) (see details in Section 2.1). Considering the data from study VAC31518COV1001 (including data on elderly), Stage 2a will be enrolled in parallel with Stage 1a, unless this is not allowed per local Health Authority guidance. Following enrollment of the initial 2,000 participants aged ≥60 years (Stage 2a), further vaccination in Stage 2 of the study will be paused to allow the DSMB to examine Day 3 safety data (ie, from Day 1 to Day 3; including

safety data from Stage 1 and the ongoing clinical studies). Upon confirmation that there are no safety concerns in this population or in the Stage 1 population up to that point, enrollment will proceed, including participants aged ≥60 years with and without comorbidities that are associated with increased risk of progression to severe COVID-19 (Stage 2b) (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 Stages 1a and 2a, that if met would result in pausing of further vaccinations (see Section 6.9), preventing exposure of new participants to study vaccine until the DSMB 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
Co-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 post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
Secondary[e] *(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], severe/critical COVID-19[b], as compared to placebo	• First occurrence of molecularly confirmed[a], severe/critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], severe/critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
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 post-vaccination

Objectives	Endpoints
	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
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, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day post-vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	• First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, 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 post-vaccination (Day 15) • First occurrence of COVID-19 requiring medical intervention and linked to any molecularly confirmed[a], COVID-19[b,c] at least 28 days post-vaccination (Day 29)
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
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 post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], mild COVID-19[c], at least 28 days post-vaccination (Day 29)
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 post-vaccination (Day 15) • First occurrence of molecularly confirmed[a] COVID-19[d] at least 28 days post-vaccination (Day 29)
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[c] (meeting the mild, moderate or severe/critical

Objectives	Endpoints
	COVID-19 case definition) with onset at least 14 days post-vaccination (Day 15). • BOD endpoint (see Section 9.5.2) derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[c] (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 28 days post-vaccination (Day 29).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination using an 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 28 days after vaccination (Day 29)
Safety	
To evaluate safety in terms of SAEs (during the entire study), MAAEs (until 6 months post-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 post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic AEs during the 7 days after vaccination, and in terms of unsolicited AEs during the 28 days post-vaccination	Occurrence, intensity, duration and relationship of solicited local and systemic AEs during the 7 days following vaccination and of unsolicited AEs during the 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA
Exploratory	
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo from Day 1 to Day 29	Serologic conversion between baseline (Day 1; pre-vaccination) and Day 29 post-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 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	• Health care utilization (such as hospitalization, ICU admission, ventilator use) linked to any

Objectives	Endpoints
molecularly confirmed[a] COVID-19, as compared to placebo	molecularly confirmed[a] COVID-19 at least 14 days post-vaccination (Day 15) • Health care utilization (such as hospitalization, ICU admission, ventilator use) linked to any molecularly confirmed[a] COVID-19 at least 28 days post-vaccination (Day 29)
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 progression to severe COVID-19, as compared to placebo	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 with onset at least 28 days after vaccination (Day 29)
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 vaccination (Day 15) • 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 28 days after vaccination (Day 29)
To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo	• Deaths occurring at least 14 days after vaccination (Day 15) • Deaths occurring at least 28 days after vaccination (Day 29)
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, as well as gene transcript profiling (RNA sequencing), 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 – Adenovirus neutralization as measured by VNA – Analysis of antibodies to S and the receptor-binding domain (RBD) of the SARS-CoV-2 S protein – SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type

Objectives	Endpoints
	virus and/or pseudovirion expressing 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 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 COVID-19 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.
To examine the degree of frailty in terms of balance in participants receiving Ad26.COV2.S vs placebo, the effect of degree of frailty on vaccine efficacy, and the degree of frailty in cases occurring in the Ad26.COV2.S vs placebo group.	Utilization of the frailty index as a measure of frailty prior to vaccination comparing the Ad26.COV2.S vs placebo group and as a measure to compare cases in the Ad26.COV2.S vaccine vs placebo group.
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 4.2 and Section 8.8).

[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] All secondary efficacy endpoint analyses will occur in the Per-Protocol (PP) analysis set, in seronegative participants unless otherwise indicated in the SAP.

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

HYPOTHESES

The study is designed to test the co-primary hypotheses of VE in the per-protocol (PP) population. For both co-primary endpoints the following hypothesis will be tested:

H0: VE ≤30% versus H1: VE >30% and each hypothesis will be evaluated at a 2.5% one-sided significance level.

The co-primary endpoints 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 vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

- 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 28 days after vaccination with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

If testing for both primary endpoint hypotheses are 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 to <60 years of age and ≥60 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 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 is safe. The sponsor has therefore decided to proceed with the single dose regimen at a 5×10^{10} vp dose level in this Phase 3 study.

The study will consist of a screening phase of up to 28 days, a 52-week double-blind study period (including the administration of 1 dose of study vaccine [on Day 1], 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 1 month. 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 2. Ad26.COV2.S will be administered at a dose level of 5×10^{10} vp.

Table 2: Vaccination Schedule VAC31518COV3001

Group	N	Day 1
1	20,000	Ad26.COV2.S (5×10^{10} vp)
2	20,000	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.

The following enrollment strategy will be used:

- Stage 1a: Initially, approximately 2,000 participants (≥18- to <60-year-old) without comorbidities that are associated with increased risk of progression to severe COVID-19 (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients) will be enrolled based on acceptable Day 29 safety and acceptable immunogenicity data, including Th1/Th2, from the corresponding age group (Cohort 1a) of the FIH study VAC31518COV1001 (see Section 2.2 for more details).
- Stage 1b: After a vaccination pause (in the age group ≥18 to <60 years of age), to allow the DSMB (also known as an independent data monitoring committee [IDMC]) to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from Stage 1a, if no safety concerns are identified enrollment will proceed, expanding enrollment to include ≥18- to <60-year-old participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19 (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).

In Stage 1, the enrollment of participants aged ≥18 to <40 years will be limited to approximately 20% of the total study population.

- Stage 2a: Initially, approximately 2,000 participants ≥60 years of age without comorbidities that are associated with increased risk of progression to severe COVID-19 will be enrolled (including approximately 1,000 Ad26.COV2.S recipients and approximately 1,000 placebo recipients). Considering the data from study VAC31518COV1001 (including data on elderly), Stage 2a will be enrolled in parallel with Stage 1a, unless this is not allowed per local Health Authority guidance.
- Stage 2b: After a vaccination pause (in the age group ≥60 years of age) to allow the DSMB to examine Day 3 safety data (ie, from Day 1 to Day 3; including safety data from Stage 1 and the ongoing clinical studies) from Stage 2a, if no safety concerns are identified in this population, enrollment will proceed, expanding enrollment to include ≥60 year-old participants with and without comorbidities that are associated with increased risk of progression to severe COVID-19 (see Section 1.2 [Figure 1] for a schematic overview of the study and Section 5.2 for the list of relevant comorbidities).

Stage 2 will enroll a minimum of approximately 30% of the total study population.

Overall, a target of approximately 40,000 adult participants (≥18- to <60-year-old and ≥60-year-old, with and without relevant comorbidities) will be randomly assigned in this study. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender.

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 DSMB. Only if both co-primary endpoints have crossed the sequential boundary, the DSMB will discuss the signal with the Oversight Group. As soon as a decision is reached, the sponsor representative on the Oversight Group will initiate internal decision procedures to trigger health authority interactions based on the outcome of the study. Sponsor personnel will be unblinded at the time of the primary analysis. If an efficacy signal is triggered before the required 8-week follow-up after vaccination for 50% of participants is reached, selected sponsor personnel will be unblinded at the time of the snapshot analysis. Further details are described in Section 9.5.1.

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 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). Biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity will also be studied (see Section 8.5). Medical resource utilization (MRU) following vaccination will be recorded for all participants with molecularly confirmed, symptomatic COVID-19 (see Section 8.6). Additional 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. 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). For consenting participants in the US, 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 Section 4.2 and Section 8.8). 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 2,000 participants in each of the 2 age groups will be closely observed at the study site for at least 30 minutes post-vaccination to monitor for the development of acute reactions If at the time of the Day 3 safety review of the initial 2,000 participants no acute reactions have been observed in the age groups, the observation period at the study site may be reduced to at least 15 minutes post-vaccination for the remaining participants in the study. 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 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 additionally 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)[63], and for MRU (such as rates of ICU admission, ventilator use).

Until 1-year post-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 post-vaccination, until the end of the 2-year follow-up period, the frequency of this surveillance question through the eCOA will decrease to once every 2 weeks. All participants will be monitored for safety (including enhanced disease) for 2 years after 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 HCP or hospital that has been identified in advance.

Any positive RT-PCR test regardless if it is obtained outside the study or at a study visit will be considered a trigger to start COVID-19 procedures. 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 or

[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.

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 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 participant's medical care provider will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

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).

A DSMB 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).

Biomarker Collection

For participants with a positive test result for SARS-CoV-2 infection, biomarker analysis (PAXgene, RNAseq) will be performed to explore potentially informative biomarkers, eg, those associated with severe COVID-19.

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)

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 to gain insight into 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 records, 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 then further encrypted using asymmetric keys in

compliance with Health Insurance Portability and Accountability Act (HIPAA).[56] 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]

For participants in the US 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 where initial immunogenicity and safety data (28 days post-Dose 1 data from Cohort 1a and available data from Cohort 3) 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 is safe. The sponsor has therefore decided to proceed with the single dose regimen at a 5×10^{10} vp dose level in this Phase 3 study.

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.

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 104 weeks post-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 administration of the study vaccine, or on the day of the 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 (1a, 1b, 2a, and/or 2b), 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. Criterion modified per Amendment 1:

   1.1 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. **Stages 1a and 1b:** Participant is ≥18 to <60 years of age on the day of signing the ICF.

   Stages 2a and 2b: Participant is ≥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 **Stages 1a and 2a:** 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 15), 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 15, the medication dose cannot have been increased within 12 weeks preceding 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 measurement at screening.

   Stages 1b and 2b: In the investigator's clinical judgement, participant may have a stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 as specified in Exclusion Criterion 15 (eg, stable/well controlled -HIV infection)*. If participants are on medication for a medical condition (including comorbidities associated with an increased risk of

[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 no pregnant women are allowed to participate in the study.

progression to severe COVID-19), the medication dose cannot have been increased within 12 weeks preceding vaccination and must be expected to remain stable for the duration of the study. Participants will be included on the basis of relevant medical history and BMI measurement at screening.

* Stable/well-controlled HIV infection includes:

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

b. Documented 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 trial.

5. Criterion modified per Amendment 1:

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

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

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 administration of study vaccine. Use of hormonal contraception should start at least 28 days before the administration of study vaccine. The investigator should evaluate the potential for contraceptive

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

method failure (eg, noncompliance, recently initiated) in relationship to the vaccination. Acceptable effective methods 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 receiving 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 study vaccine administration.
7. Participant agrees to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving 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].

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

[a] Participants with visual impairment are eligible for study participation and may have caregiver assistance in completing the eCOA questionnaires.

24 hours prior to the planned study vaccination; 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 1:

   3.1 Criterion modified per Amendment 2:

   3.2 Criterion modified per Amendment 3:

   3.3 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 participant 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 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 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 transfusions are not exclusionary) in the 4 months before the planned administration of the 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 study vaccine.

   b. Other licensed (not live) vaccines - within 14 days before or after planned administration of study vaccine.

6. Participant previously received a coronavirus vaccine.

7. Criterion modified per Amendment 1:

   7.1 Criterion modified per Amendment 2:

7.2 Criterion modified per Amendment 3:

7.3 Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19) within 30 days or used an invasive investigational medical device within 30 days or received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine or 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. Criterion modified per Amendment 1:

8.1 Participant is pregnant or planning to become pregnant within 3 months after study vaccine administration.

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. Criterion deleted per Amendment 1:

12. Criterion modified per Amendment 1:

12.1 Participant has had major psychiatric illness which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.

13. Participant cannot communicate reliably with the investigator.

14. 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.

15. Criterion modified per Amendment 1:

15.1 Criterion modified per Amendment 2:

15.2 **Stages 1a and 2a:**

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

16. **Stages 1a and 2a:** 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).
17. Criterion Modified per Amendment 2:

    17.1 Participant has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).
18. **Stages 1a and 2a:** Participant had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization, or has surgery requiring hospitalization planned during the time the participant is expected to participate in the study or within 6 months after study vaccine administration.
19. **Stages 1a and 2a:** 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 study vaccination. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the study vaccination 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.

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:

[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 no pregnant women are allowed to participate in the study.

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 Stages 1a or 2a, but does meet the criteria for participation in Stages 1b or 2b, 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:

- 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 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.

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 Ad26.COV2.S or placebo at Day 1 (see Schedules of Activities), using the same volume (ie, 0.5 mL).

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)	Placebo 0.9% Sodium Chloride
Type	Biologic/vaccine (1 dose)	Placebo (1 dose)
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	0.9% NaCl
Dosage Level(s)	**Day 1**: Ad26.COV2.S (5×10^{10} vp)	**Day 1:** 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 HCP) 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 15.

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, biomarker, 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 sponsor personnel 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 DSMB 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 safety evaluations.

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 SARS-CoV-2 vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the schedule 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 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 protocol, 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 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. 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.

At such time, an amendment will be submitted to permit individual unblinding and to determine the approach to this situation in the statistical analysis plan.

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 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 vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after 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 vaccination through 28 days after vaccination. Concomitant therapies associated with solicited AEs will be collected by the participants and recorded in the eCRF from the time of vaccination through 7 days after vaccination.

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 (including investigational drugs for prophylaxis of COVID-19) within 30 days or used an invasive investigational medical device within 30 days or received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine. 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 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 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. 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 Stages 1a and 2a

A committee consisting of the representatives of the sponsor and collaboration partners, along with the principal investigator (the protocol safety review team [PSRT]) and the Janssen Medical Safety Council will monitor safety in a blinded manner, including the study vaccination pausing rules (applicable to Stages 1a and 2a only). Adverse events that may lead to the study vaccination pausing rules (applicable to Stages 1a and 2a only) are described below and will be assessed by the Janssen Medical Safety Council to confirm that the study pause is warranted.

The occurrence of any of the following events in Stages 1a and 2a 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, in consultation with the Janssen Medical Safety Council, then decides whether a study pause is warranted and informs the DSMB of the decision. All sites will be notified immediately in the event of a study pause. The sponsor's medical monitor or designee

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

is responsible for the immediate notification of DSMB members and coordination of a DSMB meeting in the event of a study pause.

The DSMB 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 DSMB. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. The formal recommendation from the DSMB 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.

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 DSMB 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 DSMB, participant safety may be threatened.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Not applicable

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
- 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 110.0 mL for participants in the Immunogenicity Subset and 55.0 mL for the other participants. Additional blood samples (up to 35 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.

The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination.

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 Day1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and 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 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 post-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 post-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 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 8.1.1.

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, 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

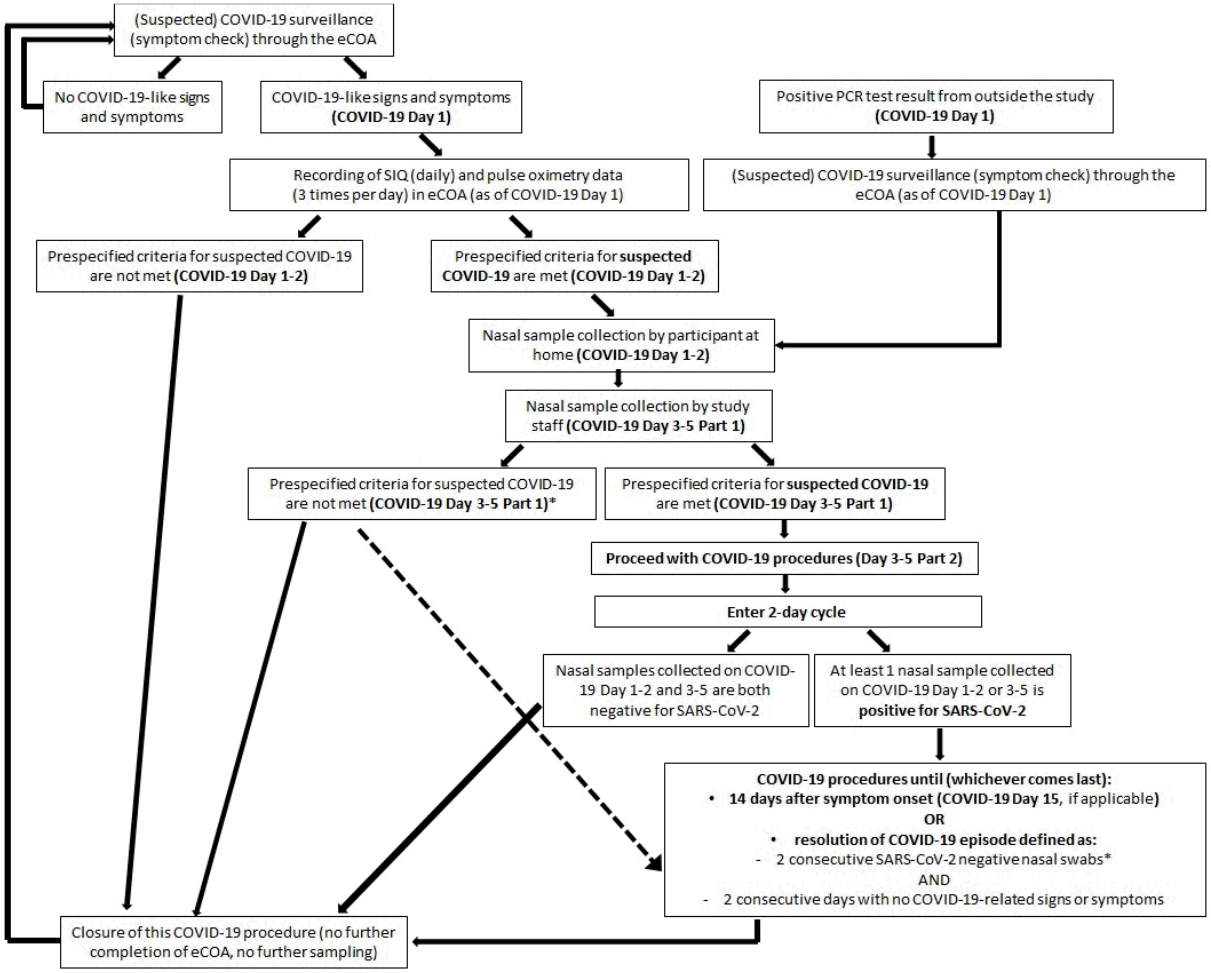
- Clinical suspicion/judgement by investigator of symptoms suggestive for COVID-19

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 site 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



If the participant no longer meets the prespecified criteria at Day 3-5 and results from the nasal sample at Day 1-2 and/or Day 3-5 are latently positive (i.e. ≥14 days to result), the participant will be contacted and asked to proceed with COVID-19 procedures (2-day cycles).

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 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 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. More 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 site 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, they 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.
- The participant will be asked to 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 with (suspected) COVID-19, 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 at least one nasal sample from COVID-19 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 exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity 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.
- <u>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>
- 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 and/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 Schedule of Activities, until the end of the study/early withdrawal.

Procedures during the 2-day cycles

If a participant has signs and symptoms that still 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 nasal sample for SARS-CoV-2 at COVID-19 Day 1-2 or COVID-19 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 Schedule of Activities, due to lack of signs and symptoms and unavailability of results from nasal swabs collected on Day 1-2 and/or 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.

  Notes:

  - 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, 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 and exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity. 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).

Notes: 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 Schedule 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 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.

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

- 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.

All potential severe/critical COVID-19 cases defined as those cases that meet the severe/critical definition by scoring of signs and/or symptoms or meet the moderate endpoint definition with a total of 3 or more signs and/or symptoms will be assessed independently by a Clinical Severity Adjudication Committee (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).

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.

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)[63] 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 (pre-vaccination), Day 71, 6 months, and 1 year after vaccination.

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

For the co-primary endpoints (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:		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

* SpO2 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[o]:

- 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])

[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).

- Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to the ICU
- Death

All cases meeting the severe/critical criteria will be adjudicated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

All cases meeting the moderate case definition and that include ≥3 signs and/or symptoms from the list of signs and symptoms will be evaluated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive.

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 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**

[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).

- 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 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination (see Section 8.1.4).

8.1.3.6. Clinical Severity Adjudication Committee

In addition to independently assessing all potential severe/critical COVID-19 cases that meet the severe/critical definition as described in Section 8.1.3.1, a blinded Clinical Severity Adjudication Committee will be established to evaluate a subset of cases of molecularly confirmed moderate to severe/critical COVID-19, for severity as part of the primary and secondary endpoints, as defined in Section 3. This committee will consist of independent clinical infectious disease experts and pulmonologists. The committee's deliberations and conclusions will be documented and will be provided to the sponsor. Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive.

8.1.4. Immunogenicity Assessments

Blood will be collected from all non-Immunogenicity Subset participants for humoral immunogenicity assessments at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after 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 on Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year, 18 months, and 2 years after vaccination.

Participants in the Immunogenicity Subset will be divided into 4 groups as presented in Table 3.

Table 3: 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	50	50	50	50
Placebo	50	50	50	50
Total	**100**	**100**	**100**	**100**

vp = virus particles
Subset 1a: healthy ≥18- to <60-year-old adults **without relevant comorbidities**, enrolled during Stage 1a.
Subset 1b: ≥18- to <60-year-old adults **with relevant comorbidities**, enrolled during Stage 1b.
Subset 2a: healthy ≥60-year-old adults **without relevant comorbidities**, enrolled during Stage 2a.
Subset 2b: ≥60-year-old adults **with relevant comorbidities**, enrolled during Stage 2b.

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 4.

Table 4: Immunogenicity and Transcriptomic 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
Transcriptomic Assay	**Purpose**
Supportive of Exploratory Objectives	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in unstimulated cells or whole blood

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; RNA = ribonucleic acid; 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 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after 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.

[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).

8.2. Safety Assessments

Details regarding the DSMB are provided in Section 9.89.8 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 PSRT and the Janssen Medical Safety Council 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, 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.

Participants in the Safety Subset will utilize an e-Diary to record body temperature measurements from the time of vaccination until 7 days post-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 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 vaccination will be collected on the Medical History eCRF page as pre-existing conditions.
- All SAEs and all AEs leading to study discontinuation (regardless of the causal relationship) are to be reported from the moment of 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 vaccination until 6 months after the 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 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 vaccination until 7 days post-vaccination.
- All other unsolicited AEs, whether serious or non-serious, will be recorded from the time of vaccination until 28 days post-vaccination.

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 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 2,000 participants in each of the 2 age groups will remain under observation at the study site for at least 30 minutes post-vaccination to monitor for the development of acute reactions. If at the time of the Day 3 safety review of the initial 2,000 participants no acute reactions have been observed in the age groups, the observation period at the study site may be reduced to at least 15 minutes post-vaccination for the remaining participants in the study.

In addition, participants in the Safety Subset will record solicited signs and symptoms in an e-Diary from time of vaccination until 7 days post-vaccination. 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 post-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 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 post-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 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. Biomarkers

During a COVID-19 episode, blood will be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 for evaluation of biomarkers (eg, those associated with severe COVID-19).

8.6. 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 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 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)

8.7. 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 the correlate analysis.

Risk factor data initially collected from participants at screening prior to implementation of Protocol Amendment 3 will also be used for the planned risk-factor analysis.

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

For consenting participants in the US, 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 (Section 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 the following timepoints for analysis:

1. The evaluation of the primary objective will be performed as soon as the target number of events (TNE) has been reached for both co-primary endpoints, or earlier based on sequential monitoring of both co-primary endpoints (details in Section 9.5.1). Sponsor unblinding will occur but investigator and participants remain blinded until study completion (end-of-study analysis). The unblinding strategy of the sponsor will be described in a separate document.

2. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached (8-week median follow-up timepoint). If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

3. After the primary analysis, additional analyses to support health authority interactions will be planned, as deemed appropriate.

4. The final analysis will be performed when the last participant completes the visit 12 months post-vaccination or discontinues earlier.

5. The end-of-study analysis will be performed when all participants have completed the visit 24 months post-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 60%.
- 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. The two

co-primary endpoints will evaluate the events at least 14 days after vaccination (Day 15) and at least 28 days after vaccination (Day 29) with study vaccine.

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 154, based on events in the active vaccination and placebo group, according to the primary endpoints case definition of moderate to severe/critical COVID-19 (Section 8.1.3.1).

If the co-primary hypothesis testing is successful for both co-primary endpoints, 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 epidemiological modeling for the targeted study countries, province/states of the various site locations, the annualized incidence of moderate to severe/critical COVID-19 cases meeting the primary endpoints definitions has been predicted to be 1.4% for the October-November timeframe. The estimate incorporates that real-world-evidence data and literature data only detected and reported a fraction of SARS-CoV-2 infections.

Furthermore, it includes that, based on literature and real-world-evidence data, only a fraction of all infections meets the moderate and severe/critical COVID-19 case definition and the fraction varies by age as well (increasing with higher ages). Moreover, projections for the selected study regions indicate that incidences will decline over time. Finally, seroprevalence rates are expected to vary between 5-15%.

For the purpose of sample size evaluation, an incidence assumption of moderate to severe/critical COVID-19 cases meeting the primary endpoints definition of 1.4% during the first 3 months of the study, with a 50% reduction in Month 4, and 62% reduction in the months thereafter is assumed in combination with a seroprevalence rate of 10%.

At the time of protocol planning, the epidemiological situation was uncertain: actual seroprevalence rates, degree of social distancing and use of personal protective equipment during the study, local regulations (eg, potential lockdowns, other vaccines if available) potentially becoming in effect during the course of the study and potential drop-outs from the study could impact the disease incidence rate.

To that end, the maximum sample size of approximately 60,000 participants was selected. This sample size was selected, based on 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 8 months of the study for a vaccine with an assumed 60% VE.

Based on an estimated case-hospitalization ratio of 2.5% and estimates obtained from reported real-world-evidence data of 3-10% of all SARS-CoV-2 infections meeting the severe/critical COVID-19 definition, this would provide a reasonable likelihood of observing 5 severe cases in the placebo group within the same time frame (8 months).

At the time of writing protocol Amendment 3, the incidence of moderate to severe COVID-19 seen in the US and reported in other COVID-19 vaccine studies is significantly higher than assumed at the time of protocol planning as described above. Furthermore, based on that incidence and modeling there is a high degree of probability that an efficacy signal meeting the prespecified criteria in this amendment will be reached at, or prior to, the time when approximately 40,000 participants will have been followed for a median of 8 weeks from the time of vaccination. Therefore, the sample size is reduced from 60,000 to approximately 40,000.

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 at each stage of the enrollment. Healthy adults (Subset 1a) will be enrolled in Stage 1a, adults with comorbidities (Subset 1b) in Stage 1b, healthy elderly (Subset 2a) in Stage 2a, and elderly with comorbidities (Subset 2b) in Stage 2b, with approximately 100 participants per group as displayed in Table 3. Although Stage 1b and 2b will also enroll participants without comorbidities, only participants with comorbidities will be included in Immunogenicity Subset 1b and Subset 2b.

A sample size of 400 participants, distributed as described in Table 3, 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.

Controls will be matched with cases from the same stage (age, comorbidities) 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 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 post-vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study. Based on a sample size of approximately 40,000 participants, and approximately 20,000 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 0.015%. Table 5 shows the probabilities of observing at least 1 event (solicited, unsolicited, or SAE) in 1 of the groups at given true AE rates.

Table 5: 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 40,000 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=20,000
0.01%	26%	86%
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 a 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: Participants in the FAS who receive study vaccine and who are seronegative at the time of vaccination 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: All randomized and vaccinated participants, 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 from participants at screening prior to implementation of protocol amendment 3 will also be used for the planned risk-factor analysis. See also Section 9.5.3.

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 Endpoints Evaluation

The study is designed to test the co-primary hypotheses of VE in the PP population. For both co-primary endpoints the following hypothesis will be tested:

H0: VE ≤30% versus H1: VE >30% and each hypothesis will be evaluated at a 2.5% one-sided significance level.

The co-primary endpoints 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 vaccination (Day 15) with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

- 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 28 days after

vaccination (Day 29) 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 for both co-primary endpoints and 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:

1. Establishing the hypothesis H1: VE>30% for each co-primary endpoint

   AND

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

To evaluate the primary null hypotheses: H0: VE ≤30% versus H1: VE >30% for the co-primary endpoints, the truncated sequential probability ratio test will be used based on accumulating event data for each co-primary endpoint. 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=60% using a one-sided alpha=0.025 against H0:VE≤30%. For the evaluation of the favorable ratio against the severe/critical COVID-19 endpoints a sequential boundary corresponding to a VE point estimate ≥50% and a minimum of 5 events in the placebo group will be prespecified. 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 with onset at least 28 days after vaccination
2. At least 42 cases meeting the primary endpoints definition of moderate to severe/critical COVID-19 with onset at least 28 days after vaccination
3. A subset of at least 5 cases meeting the primary endpoints definition of severe/critical COVID-19 with onset at least 28 days after vaccination

No interim evaluation will be done, until those conditions are fulfilled. Monitoring for efficacy will not start before the above conditions 1-3 are met and will occur at least once a week by the SSG of the DSMB until the prespecified boundaries have been crossed.

The efficacy analysis will be triggered by either:

1. a) An interim evaluation if all prespecified efficacy boundaries have been met OR if 154 cases meeting the primary endpoints definition of moderate to severe/critical COVID-19 are observed for events with onset at least 28 days after vaccination

   AND

   b) The above 3 conditions are met.

OR, alternatively,

2. If the prespecified non-efficacy boundary has been met (evaluating events with start 28 days after 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 an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

If more than 154 primary endpoints are observed for events with onset at least 28 days after vaccination before the 3 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 boundaries and above conditions are met, the SSG will inform the DSMB and, if deemed appropriate by the DSMB, a meeting with the DSMB and the Oversight Group will be set up to discuss the efficacy signal. Upon this meeting the sponsor representative on the Oversight Group can trigger internal decision procedures to initiate health authority interactions based on the outcome of the study. However, the study sites and participants will remain blinded to allow for evaluation of durability of VE. Sponsor personnel will be unblinded at the time of the primary analysis. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached (defined as “snapshot analysis”), selected sponsor personnel will be unblinded at the time of the snapshot analysis. The unblinding strategy of the sponsor will be described in a separate document.

The primary efficacy analysis will pool data across populations (both age groups with and without comorbidities) to evaluate the primary and secondary objectives. In addition, these will be supplemented with a subgroup analysis for age group (18 to <60 years, ≥60 years) and comorbidities employing a descriptive summary including 95% confidence intervals to describe

the VE in each subpopulation. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (≥70 years, ≥80 years).

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%]. Divergence of vaccine and placebo curves may be utilized to estimate onset of efficacy following immunization.

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

9.5.1.1. Study Monitoring

Table 6: 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 (Day 15)[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 42nd event[c] 14 days post-dose (Day 15), **then at least once a week**
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 42nd event[c] 28 days post-dose (Day 29), **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 DSMB and a DSMB 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 DSMB 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 $T = X_1 + X_2 =$ 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 vaccination (Day 15) and with onset at least 28 days after vaccination (Day 29) 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.

VE against severe/critical infections with onset at least 14 days after vaccination (Day 15) and with onset 28 days after vaccination will be evaluated. Exact Poisson regression will be used to estimate the VE and associated confidence interval in seronegative participants in the PP analysis set.

The co-primary endpoints and BOD endpoint will be evaluated at the time of efficacy signal, and again at the time when the 8-week median follow-up requirement is reached (should the efficacy signal occur earlier).

VE against any SARS-CoV-2 infection and against asymptomatic infections will be evaluated as soon as a sufficient number of participants have data available. This timepoint will be detailed in the statistical analysis plan and may occur at any of the planned analysis timepoints. Available N-ELISA measurements will be incorporated to evaluate VE against any infection, including asymptomatic infection and against asymptomatic/undetected infection only. 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). Poisson regression will be used to estimate the VE and associated 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 for events with onset at least 14 days after vaccination and with onset at least 28 days after vaccination. 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. Exact Poisson regression will be used to estimate the VE and the associated confidence interval in seronegative participants in the PP analysis set.

All VE evaluations will be repeated regardless of their serostatus.

Supportive and/or descriptive analysis will be reported with 95% confidence intervals; confirmatory endpoints will have an adjusted confidence interval reported at the time of hypothesis testing whereby the alpha level is determined according to the FWER-controlled testing strategy.

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

Biomarkers Analyses

Exploratory biomarker analyses will be part of a separate report.

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

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. More 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 post-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 a DSMB (also known as an IDMC). In general, the DSMB 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 1a (2,000 participants) and stage 2a (2,000 participants). The DSMB will review unblinded data. The DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter.

The DSMB will also review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

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 DSMB through secure communication procedures. At this point the DSMB will convene and provide a recommendation to the Oversight Group, which includes a sponsor representative as a core member. 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 DSMB 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 DSMB will evaluate in an unblinded fashion whether superiority is established for the primary endpoints 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 endpoints 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 DSMB will contain unblinded events and a report provided to the sponsor will contain blinded events. While it is the primary responsibility of the sponsor to make decisions regarding study operations and modifications based on monitoring of study vaccine-blinded primary events from the study, the DSMB can evaluate the progress towards primary endpoints targets in the context of the study vaccine-unblinded data,

and based on this review may recommend to the Oversight Group, which includes a sponsor representative as a core member, to complete the study early due to reaching the boundaries for efficacy or non-efficacy to assess VE (see Section 9.5.1).

The monitoring rules will be detailed in the DSMB 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 SARS-CoV-2 vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the schedule 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
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
MSD	Meso Scale Discovery
N	nucleocapsid
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
PA	primary analysis
PaO_2	partial pressure of oxygen
PP	Per-protocol (efficacy)
PPI	Per-protocol Immunogenicity
PQC	product quality complaint
PSRC	Prevention Science Review Committee
PSRT	protocol safety review team
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.[58,59]
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 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 (prior to vaccination) (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)

	• Serum samples for humoral immunogenicity	• Non-Immunogenicity Subset: on study visits 2, 3, 4, 5, and 6 and the early exit visit (if applicable) • Immunogenicity Subset: on study visits 2, 3, 4, 5, 6, 7, and 8, and the early exit visit (if applicable)
	• Serum sample for sero-confirmation of past SARS-CoV-2 infection	• On Day 1 (pre-vaccination), Day 29, Day 71, 6 months, and 1 year after vaccination • COVID-19 Day 29
	• Serum sample for humoral immunogenicity	• On COVID-19 Day 3-5 and COVID-19 Day 29
	• RNAseq blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity (PAXgene tubes, whole blood)	• On Day 1, Day 29, 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 biomarker and 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

A DSMB (also known as 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 1a (2,000 participants) and stage 2a (2,000 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.

The DSMB will also review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

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 DSMB of any AE of concern.

If the SSG assesses that the stopping boundary is met (see below), the Chair of the DSMB will immediately be informed through secure communication procedures. At this point, the DSMB will

convene and provide a recommendation to the Oversight Group, which includes a sponsor representative as a core member.

In addition, the DSMB will formally monitor the infections in all groups to conclude both non-efficacy and efficacy. The DSMB will evaluate in an unblinded fashion whether superiority is established for the primary endpoints 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 PSRT and the Janssen Medical Safety Council review all clinical and laboratory safety data during the course of the study.

Statistical Support Group

The SSG is the statistical support group to the DSMB; they are unblinded and provide the DSMB with the statistical analysis based on unblinded data. As the DSMB, 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 DSMB through secure communication procedures. At this point the DSMB will convene and provide a recommendation to the Oversight Group, which includes a sponsor representative as a core member. 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 Severity Adjudication Committee

All potential severe/critical COVID-19 cases defined as those cases that meet the severe/critical definition by scoring of signs and/or symptoms or meet the moderate endpoint definition with a total of 3 or more signs and/or symptoms will be assessed independently by a Clinical Severity This committee will independently evaluate the severity of the COVID-19 cases in a blinded manner. The committee will consist of independent clinical infectious disease experts and a pulmonologist. The committee's deliberations per case and conclusions will be documented and will be provided to the sponsor. For more details on this committee, refer to Section 8.1.3.6.

Oversight Group

The Oversight Group's responsibilities, authorities, procedures and their interactions with the DSMB will be documented in the Oversight Group 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 h and i 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 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: _____

[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.

VITAL SIGNS
Has vital sign assessment been performed? □ **Yes** □ **No** **Temperature (ºC/ºF): _____** **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 SpO2 ≤93% on room air at sea level[a] or PaO2/FiO2 <300 mmHg)**
  □ **Yes** □ **No**
  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 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:** _____

[a] SpO_2 criteria will be adjusted according to altitude per investigator judgement.

- **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? *If 'yes' selected, please fill out remaining questions in this section.*	□ **Yes** □ **No**

Type of supplemental oxygen administration:

□ **Invasive Mechanical Ventilation** □ **Venturi Mask**

□ **Non-Invasive Mechanical Ventilation** □ **Simple Face Mask**

□ **Nasal Cannula** □ **Reservoir Cannulas**
□ **Nonrebreathing Face Mask with Reservoir and One-Way Valve**

□ **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 for COVID-19 performed? □ **Yes** □ **No**
If yes, please specify: ▪ **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

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

10.13. 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 (29 October 2020)

Overall Rationale for the Amendment: This 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. Also, some errors, have been corrected, including the clarification that blood will be drawn on Day 29 for biomarker RNAseq analyses (PAXgene tube), which is needed in order to assess the current objectives. Finally, some minor errors have been corrected.

The changes made to the clinical protocol of study VAC31518COV3001 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 8.1.1 Prespecified Criteria for Suspected COVID-19 8.1.2 Procedures in the Event of (Suspected) COVID-19 8.1.3.4 Case Definition for Asymptomatic or Undetected COVID-19 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.
1.3.1 All Participants 8 STUDY ASSESSMENTS AND PROCEDURES 10.2 Appendix 2: Clinical Laboratory Tests	It has been clarified that at Day 29 2.5 mL blood will be collected from participants for biomarker RNAseq analyses (PAXgene tube).	Correction. In order to assess the objectives as currently stated in the protocol, a blood sampling for biomarker RNAseq (PAXgene) performed after the participants have received the vaccination is required.
1.1 Synopsis 2.1 Study Rationale 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design 9.2.2 Immunogenicity Subset	It has been clarified that Stage 1b and Stage 2b will enroll participants with and without comorbidities. However, participants in the Immunogenicity Subset 1b and 2b will be participants with comorbidities.	Clarification
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	The specification of '(>10 days)' when referring to the chronic use of systemic corticosteroids has been	To remove ambiguity as within the same exclusion criterion 3 a substantial immunosuppressive steroid dose is defined as ≥2

Section Number and Name	Description of Change	Brief Rationale
	removed from the exclusion criterion 3.	weeks of daily receipt of 20 mg of prednisone or equivalent
1.3.1 All Participants 1.3.2 Participants With (Suspected) COVID-19 8.6 Medical Resource Utilization 10.8 Appendix 8: Medically-attended COVID-19 (MA-COV) Form	The MA-COV form has been updated to also capture if a participant has clinical or radiological evidence of pneumonia 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.
10.3.11 Monitoring	Source data verification has been replaced by review of the source data.	Source document review will be done instead of source document data verification.
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 VAC31518COV3001.
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 VAC31518COV3001 as pregnant women are not allowed to participate in the study.
9.5.1.1 Study Monitoring	Clarified that there will be no adjustment for multiple testing for the potential harm monitoring of severe cases, ie, an exact 1-sided binomial test of the fraction of infections assigned to who receive the vaccine will be used with an unadjusted p-value α at 5%.	Adjusted in line with HA feedback to start monitoring of severe events as soon as 5 events and subsequently after every new event without adjustment for multiple testing
1.1 Synopsis 1.3.1 All Participants 1.3.2 Participants With (Suspected) COVID-19 4.1 Overall Design 8.7 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 and	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
	6 months and 1 year post vaccination and at COVID-19 Day 3-5.	
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	Exclusion criterion 7 was adjusted to exclude participants who received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months.	Alignment across Ad26.COV2.S Phase 3 study protocols
5.2 Exclusion Criteria	Chronic kidney disease (with dialysis) has been removed from the examples of clinical conditions expected to have an impact on the immune response of the study vaccine.	There is no evidence that dialysis has an impact on antibody concentration in the blood.
1.1 Synopsis 5.2 Exclusion Criteria	It is clarified Parkinson's disease, seizures, ischemic strokes, intercranial hemorrhage encephalopathy, meningoencephalitis are not part of the CDC list of comorbidities that are associated with increased risk of progression to severe COVID-19.	Clarification
5.2 Exclusion Criteria	It is clarified that participants with Guillain-Barré syndrome are excluded from the study altogether and not only in Stage 1a and Stage 2a of the study.	Correction
5.1 Inclusion Criteria	Clarifications have been made to the inclusion criterion 4, indicating that for Stages 1a and 2a participants can have a condition that is stable and well controlled except the ones listed in exclusion criterion 15 which are associated with increased risk of progression to severe COVID-19. In addition, medication dose for allowed stable conditions (in all stages of the study) cannot have been increased within 12 weeks prior to vaccination.	Clarification
5.4 Screen Failures	It has been clarified that participants can be rescreened once, also when they meet all in- and exclusion criteria but	To allow participants who were found eligible to be enrolled in the study but were not randomized within the 28-day

Section Number and Name	Description of Change	Brief Rationale
	the 28-day screening period was exceeded.	screening window to still participate in the study.
1.1 Synopsis 9.8 Interim Analysis and Committees	Reference to a possible sample size adjustment has been deleted.	Correction; per the VAC31518COV3001 Amendment 1, the sample size of approximately 60,000 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 10.8 Appendix 8: Medically-attended COVID-19 (MA-COV) Form	It has been clarified that the adjustment according to altitude for the SpO2 criteria is per the investigator judgement.	Clarification

Section Number and Name	Description of Change	Brief Rationale
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.
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. Addition of minor clarifications. Alignment across sections in the protocol.

Amendment 1 (15 September 2020)

Overall Rationale for the Amendment: The amendment is written to adjust the dose level for Ad26.COV2.S from 1×10^{11} virus particles (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. Additional changes such as the determination of the sample size, further fine tuning of the case definitions for COVID-19, and the addition of target percentages (min/max) for enrollment of certain age groups are made based on emerging epidemiology information and advancing insights. 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 VAC31518COV3001 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 4.4 End-of-study Definition 4.3 Justification for Dose 6.1 Study Vaccines Administered 8.1.4 Immunogenicity Assessments	The Ad26.COV2.S dose level has been lowered 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

[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
		≥20%. This finding was supplemented 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 for proceeding to Phase 3 were met by the $5x10^{10}$ vp dose, the sponsor decided to use this dose for further evaluation in the Phase 3 study VAC31518COV3001.
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design 9.2.1 Efficacy (Total Sample Size) 9.2.4 Safety (Safety Subset)	The protocol has been adjusted to reflect the selected sample size of approximately 60,000 participants. A detailed rationale for the sample size selection has been added to Section 9.2 Sample Size Determination of the protocol.	Based on epidemiological modeling and currently available data (further explained in Section 9.2.1), the maximum sample size of 60,000 participants was selected.
1.1 Synopsis 9.5.1 Primary Endpoint Evaluation	The trigger for the evaluation of the primary endpoint has been modified, adding 3 conditions, one related to available follow-up information, one related to the number of severe/critical COVID-19 cases and one related to the number of cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 in the elderly population, that need 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.
1.1 Synopsis 1.3.1 All Participants 3 OBJECTIVES AND ENDPOINTS 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.4 Immunogenicity Assessments 9.2.1 Efficacy (Total Sample Size) 9.5.1 Primary Endpoint Evaluation 9.5.2 Secondary Endpoints 9.5.1.1 Study Monitoring 10.2 Appendix 2: Clinical Laboratory Tests	The time to begin counting COVID-19 cases after vaccination with Ad26.COV2.S has been decreased from at least 28 days post-vaccination to at least 14 days post-vaccination (Day 15).	Based on preliminary data from Cohort 1b of study VAC31518COV1001, showing robust immunology data 14 days after vaccination that are similar to the data seen 28 days after vaccination.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design 9.2.1 Efficacy (Total Sample Size) 9.5.1 Primary Endpoint Evaluation	The assumed vaccine efficacy (VE) has been adjusted from a VE=65% VE to a 60%=VE. The target number of events (TNE) has been adjusted accordingly from 104 to 154 events	The study power was adjusted to have approximately 90% power to detect an assumed vaccine efficacy as low as 60%, in line with Health Authority guidance. The target number of events has been adjusted accordingly.
1.1 Synopsis 1.2 Schema 2.1 Study Rationale 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design 9.2.2 Immunogenicity Subset	It has been clarified that Stage 2a (adults ≥60 years of age) can start in parallel to Stage 1a (adults ≥18 to <60 years of age) unless this is not allowed per local Health Authority guidance.	After a review of the currently available safety and immunogenicity data from Cohort 1a and Cohort 3 of study VAC31518COV1001 (see above), staggered enrollment of Stage 2 is no longer deemed necessary.
5.1 Inclusion Criteria 5.2 Exclusion Criteria	A clarification was added to the eligibility criteria on blood pressure for Stage 1a and Stage 2a.	Following discussion with the agency on the VAC31518COV1001 protocol, it was agreed that the blood pressure criteria from the CDC list of comorbidities associated with COVID-19 progression could be modified. The VAC31518COV3001 protocol has been harmonized with the VAC31518COV1001 protocol.
1.1 Synopsis 5.1 Inclusion Criteria 5.2 Exclusion Criteria 10.10 Appendix 10: Symptoms of Coronavirus (US Centers for Disease Control and Prevention)	It has been clarified that the current list of CDC comorbidities applicable to the in- and exclusion criteria will not be adjusted during the conduct of the study even if the source CDC list is updated.	Changing the CDC list of comorbidities during the study would be operationally very difficult and should not be required since they are only used in the initial part of the study, ie, in enrollment of the first 2,000 participants in each of the age groups, which will occur only a few weeks apart.
1.3.1 All Participants 5.1 Inclusion Criteria 5.2 Exclusion Criteria 8.4 Virology Assessments 9.7 Safety Analysis	The eligibility criteria, HIV RNA viral load and CD4 cell count assessment and subanalyses of the data related to HIV positive participants in this study has been updated.	To provide objective criteria for stable/well-controlled HIV infection and details regarding this subpopulation on various other study aspects.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 9.2.3 Immunogenicity Correlates (Correlates Subset) 9.5.2 Secondary Endpoints	The endpoint used to assess the effect of Ad26.COV2.S on all molecularly confirmed symptomatic COVID-19, as compared to placebo was adjusted to the Burden of Disease endpoint.	Following a Health Authority question on how the different groups of mild, moderate and severe COVID-19 cases will be analyzed, the Burden of Disease (BOD) secondary endpoint has been added to the protocol. The BOD endpoint will be evaluated based on the first occurrence of molecularly confirmed COVID-19, including mild, moderate and severe/critical case definitions.
1.1 Synopsis 9.5.1 Primary Endpoint Evaluation 9.5.1.1 Study Monitoring 9.8 Interim Analysis and Committee(s)	The severe harm monitoring rule has been modified to indicate that monitoring will start from the 5th severe event onwards instead of the 8th severe event and monitoring will be done until the primary analysis is triggered instead of until the end of the study. In addition, monitoring for efficacy will start from the 20th event onward at least once a week instead of after each event.	Based on Health Authority request to start monitoring earlier.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 9.5.2 Secondary Endpoints	It has been clarified that all secondary endpoint analyses will occur in the per protocol analysis set, in seronegative participants unless otherwise indicated.	To clarify the analysis set used to evaluate the secondary endpoints.
1.1 Synopsis 8.1.3.1 Case Definition for Moderate to Severe/Critical COVID-19 8.1.3.2 Case Definition for Mild COVID-19	The case definitions of both mild and moderate COVID-19 have been modified and terminology has been aligned across case definitions.	To incorporate additional key conditions in the case definition of mild disease and for clarification purposes.
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.
4.2.1 Study-Specific Ethical Design Considerations 6.6 Continued Access to Study Vaccine After the End of the Study	It has been clarified that the sponsor will also look into the possibility of offering placebo recipients the study vaccine, if this vaccine is determined to be efficacious, considering country-specific conditions and ethical considerations.	Based on a partner request to clarify the plans of providing vaccine, if it is determined to be efficacious, to participants who received placebo.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	It has been clarified that every effort will be made to avoid inclusion of participants who have been previously enrolled in coronavirus studies and to prevent subsequent enrollment of a participant in other coronavirus studies during their participation in this study.	To ensure that co-enrollment in other efficacy studies is avoided.
1.1 Synopsis 8.1.3.4 Case Definition for Asymptomatic or Undetected COVID_19 8.1.3.5 SARS-CoV-2 Seroconversion Assessment	A subsection on case definition of asymptomatic or undetected COVID-19 and SARS-CoV-2 seroconversion assessment has been added to the Efficacy Assessment section.	To clarify what is considered an asymptomatic infection.
5.2 Exclusion Criteria	It has been clarified that planning to become pregnant within 3 months after study vaccine administration will lead to exclusion from participation in the study.	For clarification purposes.
1.1 Synopsis 8.1.4 Immunogenicity Assessments	It has been added that serology testing outside the study is discouraged and if testing would be needed, the site will guide the participant to an appropriate assay.	Vaccination with Ad26.COV2.S may interfere with some serologic assays utilized at local community health clinics/commercial laboratories and may result in unblinding the participant.
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 in the prestudy and concomitant therapy section of the protocol.	To clarify that antipyretics are recommended post-vaccination for symptom relief, as needed. Prophylactic antipyretic use is not encouraged.
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 2,000 participants in each of the 2 age groups and may be decreased to 15 minutes for the remaining participants, if no acute reactions are observed.	To decrease the burden for the participant and for clarification purposes.
1.1 Synopsis 4.1 Overall Design 8.1.4 Immunogenicity Assessments	It has been clarified that the participant will be notified of a confirmed positive SARS-CoV-2 infection and positive serology test.	For clarification purposes.
6.2 Preparation/Handling/Storage/Accountability 6.4 Study Vaccine Compliance	It has been clarified that the unblinded pharmacist cannot vaccinate participants.	Administration of the vaccine by an unblinded pharmacist is not permitted.

Section Number and Name	Description of Change	Brief Rationale
8.1.2 Procedures in the Event of COVID-19-like Signs and Symptoms	It has been clarified that the study staff visiting participants at home will use personal protective equipment according to local regulations.	Based on partner recommendations to include protective measures for site staff visiting participants at home.
8.2.2 Vital Signs	It has been clarified that any vital signs measures 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.	Based on a partner request to clarify if a participant with a positive test will be referred to a health care provider.
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: Baseline Risk Factor Assessment	It has been added that additional baseline and 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.
5.2 Exclusion Criteria	Exclusion of participants with drug or alcohol abuse has been removed from exclusion criterion 12.	To avoid redundancy as this is also covered in exclusion criterion 14.
1.1 Synopsis 9.1 Statistical Hypotheses	It has been clarified that additional analyses after the primary analysis can be planned, if deemed appropriate.	For clarification purposes.
1.1 Synopsis 3 Objectives and Endpoints 8.1.4 Immunogenicity Assessments	An exploratory immunogenicity objective/endpoint and respective assays have been added to assess other coronavirus immune responses at baseline.	To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity.
2.3.1 Risks Related to Study Participation 5.2 Exclusion Criteria	It has been clarified that breastfeeding women can participate in the study.	To allow the enrollment of breastfeeding women in the study, as the risk of getting infected outweighs the risk of exposing the child to vaccine induced antibodies.

Section Number and Name	Description of Change	Brief Rationale
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 participants ≥60 years of age has been adjusted to 30%.	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-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.
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	In the exclusion criteria and the concomitant medication section, it has been further clarified that the use of any investigational or approved COVID-19 vaccine (other than Ad26.COV2.S) is disallowed at any time prior to and during the study.	Clarification of an inconsistency and alignment across sections within the protocol.
1.1 Synopsis 1.3.1 All Participants 3 OBJECTIVES AND ENDPOINTS 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.3 Efficacy Assessments 8.1.4 Immunogenicity Assessments 10.2 Appendix 2: Clinical laboratory Tests	Blood draws for immunologic testing for SARS-CoV-2 seroconversion (ELISA and/or SARS-CoV-2 immunoglobulin assay) based on SARS-CoV-2 N protein, have been added on Day 71 and 6 months in order to identify cases of asymptomatic infection. Visit 4 has therefore become a mandatory visit for all participants.	To allow for the identification of a possible signal for the prevention of asymptomatic infection at earlier timepoints.
1.3.1 All Participants 1.3.2 Participants With COVID-19-like Signs and Symptoms 2.3.1 Risks Related to Study Participation 8 Study Assessments and Procedures 8.1.2 Procedures in the Event of COVID-19-like Signs and Symptoms 10.2 Appendix 2: Clinical Laboratory Tests 10.8 Medically-attended COVID-19 (MA-COV) Form	The term "mid-turbinate" in relation to the nasal swabs collection has been removed throughout the protocol.	To remove any confusion around the type of swabs used during the study as the swabs currently used are not mid turbinate swabs but their performance can be considered equivalent.

Section Number and Name	Description of Change	Brief Rationale
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.
1.1 Synopsis 1.3.1 All Participants 4.1 Overall Design	It has been clarified that enrolled participants will be counselled on SARS-COV-2 infection prevention. In addition, it is clarified that at the time of study entry, each participant will need to indicate to the study site where, 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.	For clarification purposes.
1.3.2 Participants With COVID-19-like Signs and Symptoms 8.1.2 Procedures in the Event of COVID19-like Signs and Symptoms 10.3.3 Informed Consent Process	It has been clarified that the caregiver can only assist with the eCOA.	To provide clarity on the roles and responsibilities of the caregiver.
1.3.2 Participants With COVID-19-like Signs and Symptoms 8.1.2 Procedures in the Event of COVID19-like Signs and Symptoms	Term "episode" was added to include all aspects of the COVID-19 illness.	For clarification purposes.
5.1 Inclusion Criteria 8.3 Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, and Other Safety Reporting 10.3.3 Informed Consent Process 10.3.4 Data Protection	References to a legally Acceptable Representative being allowed to provide consent instead of the potential participant has been removed from the protocol.	A participant needs to fully understand and be able to provide consent themselves given there may be no benefit to participation. Participants unable to consent for themselves should not be enrolled in the study.
1.1 Synopsis 2.1 Study Rationale 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design 9.8 Interim Analysis and Committee(s) 10.3.6 Committees Structure	Reference to Grade 4 AEs and SAEs in the context of Day 3 safety review by the DSMB has been deleted from the protocol.	The DSMB review of the Day 3 safety data from Stage 1a and 2a prior to enrollment of Stage 1b and 2b, respectively, will not be limited to Grade 4 AEs and SAEs. All available safety data will be reviewed.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design 9.5.1 Primary Endpoint Evaluation 9.8 Interim Analysis and Committee(s) 10.3.6 Committees Structure	The role of the Sponsor Committee has been replaced either by the role of the Oversight Group (as described in the Oversight Group Charter) or the role of the sponsor.	For clarification purposes.
2.3.1 Risks Related to Study Participation	Influenza will not be used as a control in the surveillance system for detection of COVID-19.	Influenza may not serve as a good positive control due to social distancing measures and the need for significant sampling to have a valid comparison.
6.9 Study Vaccination Pausing Rules for Stages 1a and 2a	It has been clarified that based on the pausing criteria, the sponsor's medical monitor or designee decides whether a study pause is warranted and informs the DSMB of the decision, instead of the PSRT deciding whether a pausing rule is warranted.	For clarification purposes.
9.5.2 Secondary Endpoints	It has been clarified that among participants with SARS-CoV-2 infection, the effect of vaccination 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.	For clarification purposes.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	The exploratory efficacy objective assessing both symptomatic and asymptomatic infections combined, (that are serologically and/or molecularly confirmed) compared to placebo has been moved to the secondary objectives.	This endpoint was moved to secondary as it will be included in the inferential testing strategy.
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.
1.1 Synopsis 8.1.4 Immunogenicity Assessments	Analysis of neutralizing antibodies to SARS-CoV-2 using a reporter SARS-CoV-2 virus has been added.	To add a new assay that may become available.
10.7 Appendix 7: MRU Questionnaire	Clarifications were made in the MRU Questionnaire.	For clarification purposes

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Addition of minor clarifications.

11. REFERENCES

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INVESTIGATOR AGREEMENT

VAC31518 (JNJ-78436735) Clinical Protocol VAC31518COV3001 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 intervention, 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: _____

Telephone Number: _____

Signature: _____ Date: _____ (Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Jerald Sadoff, MD

Institution: Janssen Research & Development

Signature: PPD Date: 14 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.

Status: Approved, Date: 14 December 2020

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 184

Status: Approved, Date: 14 December 2020

Janssen Research & Development

Statistical Analysis Plan

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

Protocol VAC31518COV3001; Phase 3

VAC31518 (JNJ-78436735)

Status:	Final
Date:	18 Sep 2020
Prepared by:	Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study
Document No.:	EDMS-RIM-137421

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

Confidentiality Statement

The information provided herein in connection with OTA No. HHSO100201700018C herein, is considered JRD, LLC trade secrets, commercial or financial information that JRD, LLC customarily holds close and treats as confidential. The information is being provided under the assurance that the U.S. Department of Health and Human Services and all of its agencies, including the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, will maintain the confidentiality of the information under the Trade Secrets Act, Procurement Integrity Act, other applicable statutes, regulations, rules, case law contractual provisions, protective orders or otherwise and as such, the information provided herein is exempt from disclosure under Exemption 4 of the Freedom of Information Act ("FOIA"). TLP: Amber for OWS use only.

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	23AUG20	Not Applicable	Initial release
2	18SEP20	CTP Amendment 1	CTP Amendment 1

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analysis methods for evaluation of the primary, secondary and exploratory objectives of the phase 3 study designed to assess in a randomized, double-blind, placebo-controlled manner the efficacy and safety of the Ad26.COV2.S candidate vaccine.

The vaccine has been designed for the prevention of SARS-CoV-2 mediated coronavirus disease 2019 (COVID-19) in adults aged 18 years and older. This SAP will detail the analytical plan for interim monitoring as well as the statistical methods for the primary analysis based on all available data at the time of data base cut off. At this time Sponsor unblinding will occur, as soon as the data base for the primary analysis is locked. Investigator and participants remain blinded until study completion (end-of-study analysis).

This analysis plan also includes the technical details for the statistical analysis plan associated with the interim monitoring evaluation for harm, non-efficacy and efficacy to support the data and safety monitoring board (DSMB).

This randomized, placebo-controlled clinical trial is designed to enable expeditious safety, efficacy and immunogenicity evaluation of the Ad26.COV2.S candidate preventive vaccine against COVID-19 at sites with high COVID-19 attack rates, to ensure the observation of COVID-19 cases to assess the role of a vaccine in containing the pandemic. Boundaries are set up to monitor for excess harm, non-efficacy and efficacy. If a prespecified boundary is met, the statistical support group (SSG) will inform the DSMB. The DSMB will provide a recommendation to the Oversight Group. The Oversight Group can trigger decision procedures to initiate health authority interactions based on the outcome of the study. If deemed appropriate based on the data, the Oversight Group may instruct a designated unblinded team independent of the study team (including a clinician, a statistician, a statistical programmer, and a regulatory person) through a secured manner, to meet regulatory requirements for submission and review by competent authorities and regulatory agencies. The study team will remain blinded until the data base for the primary analysis is locked.

The primary objective of the trial is to evaluate the vaccine's effect on the rate of virologically-confirmed moderate to severe/critical COVID-19, in adults at high risk for infection and/or disease. The trial will enroll and randomize large numbers of adult participants in different populations. Until 1 year post-vaccination or until the primary analysis takes place (whichever comes last), 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 post-vaccination or after the primary analysis takes place (whichever comes last), until the end of the long-term follow-up period, the frequency of this surveillance question through the eCOA will decrease to once every 2 weeks.) Vaccine efficacy to prevent mild COVID-19, to prevent COVID-19 of any severity (burden of disease), to prevent acquisition of asymptomatic SARS-CoV-2 infection, to prevent COVID-19 requiring medical intervention, to prevent acquisition of any SARS-CoV-2 infection and to investigate SARS-CoV-2 viral load for moderate to severe/critical COVID-19 cases are secondary objectives.

The design has continuous monitoring of events to report results upon early evidence of vaccine efficacy, lack of efficacy, or vaccine safety concerns. The trial is powered to provide sufficient evidence of safety and vaccine efficacy to prevent COVID-19 in support of possible (potential) marketing authorizations. The sample size can be modified when the study is still recruiting based on pertinent background information on for example predicted COVID-19 attack rates and blinded data. Due to the speed of planned recruitment it is considered unlikely that the sample size will be modified.

1.1. 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 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 post-vaccination (Day 15)
Secondary [e]	
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 post-vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15)
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, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit [ICU] admission, mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomographic [CT] findings) or linked to any molecularly confirmed[a], COVID-19[b,c] at least 14 days post-vaccination (Day 15)
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
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[b], at least 14 days post-vaccination (Day 15)

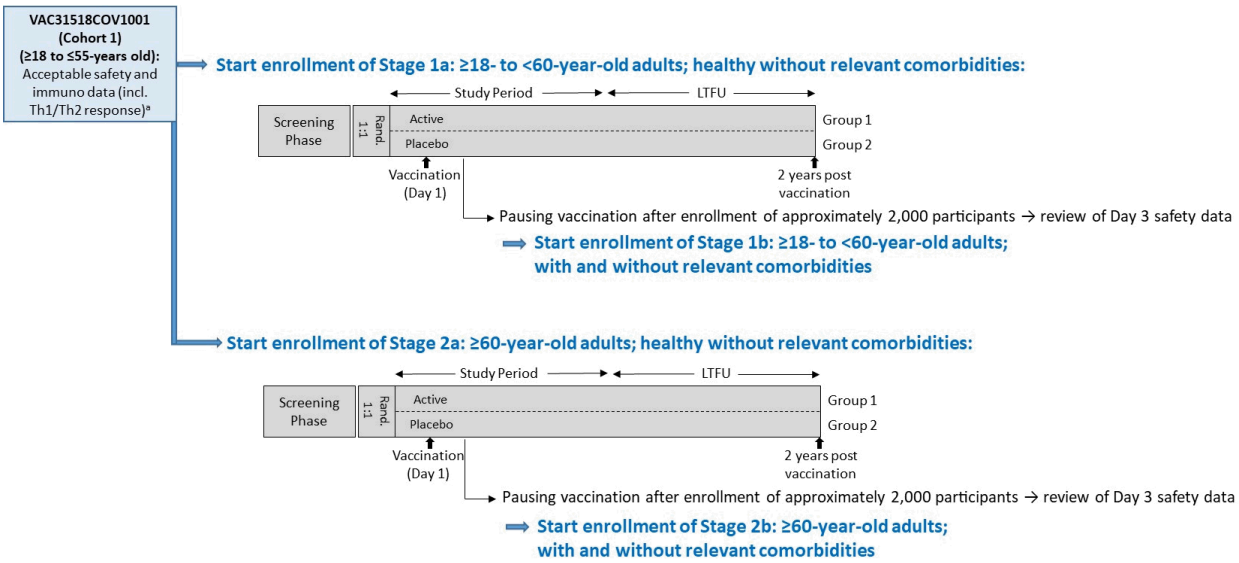
Objectives	Endpoints
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition[d]	First occurrence of molecularly confirmed[a] COVID-19[b] at least 14 days post-vaccination (Day 15)
To assess the effect of Ad26.COV2.S on all molecularly confirmed[a] symptomatic COVID-19 [b,c], as compared to placebo	Burden of disease (BOD) endpoint [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 post-vaccination (Day 15).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed[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 vaccination (Day 15)
Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination, and in terms of unsolicited AEs during 28 days post-vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days following vaccination and of unsolicited AEs during 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	– Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA – SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein)

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result 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 in the CTP).
[c] Per case definition for mild COVID-19 (see Section 8.1.3.2 in the CTP).
[d] Per case definition for COVID-19 according to the US FDA harmonized case definition (see Section 8.1.3.3 in the CTP).
[e] All secondary endpoint analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated.
[f] For more information and the definition of the BOD endpoint, refer to the Section 9.5.2 Secondary Endpoints in the CTP.

1.2. Study Design

This is 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. An overview of the design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Participants will be vaccinated with one vaccination according to a 1:1 randomization:

- 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 Ad26.COV2.S or placebo at Day 1, using the same volume (ie, 0.5 mL).

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 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 15 (see CTP).

The randomization system will be used to control the age distribution of participants in the trial; in particular the age ranges of ≥18 to <40 and ≥40 to <60 years can be closed separately for further

randomization in order to obtain a distribution of approximately 20% and 50% for these age ranges, respectively, and to have a minimum of approximately 30% of the population to be ≥60 years.

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.

2. STATISTICAL HYPOTHESES

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 in the CTP), with onset at least 14 days post vaccination with Ad26.COV2.S or placebo, in the PP population, including all events from both age groups, with and without comorbidities.

A successful primary efficacy conclusion will require:

1. Establishing the hypothesis H1: VE>30% for the primary endpoint. The study is designed to test the primary hypothesis of vaccine efficacy (VE) against moderate to severe infections in the PP set: H_0: VE ≤30% versus H_1: VE >30% and will be evaluated at a 2.5% one-sided significance level.

   AND

2. A favorable split vaccine:placebo for the subset of primary endpoints meeting the severe/critical COVID-19 case definition (expressed as a VE point estimate against severe/critical COVID-19 molecularly confirmed endpoints ≥50%) and a minimum of 5 events in the placebo group.

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=60% using a one-sided alpha=0.025 against H0:VE≤30%, with appropriate control of the type-1 error rate (alpha) for interim monitoring.

For the evaluation of the favorable ratio against the severe/critical COVID-19 endpoints a sequential boundary corresponding to a VE point estimate ≥50% and a minimum of 5 events in the placebo group will be prespecified. This is further detailed in section 5.3.3.

If the primary endpoint hypothesis testing reaches significance, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%.

For each secondary endpoint in the confirmative endpoint section 5.4.2, the hypothesis of vaccine efficacy (VE) H_0: VE ≤0% versus H_1: VE >0% will be evaluated in the PP set, including all events with onset 14 days post vaccination at the time of the primary analysis.

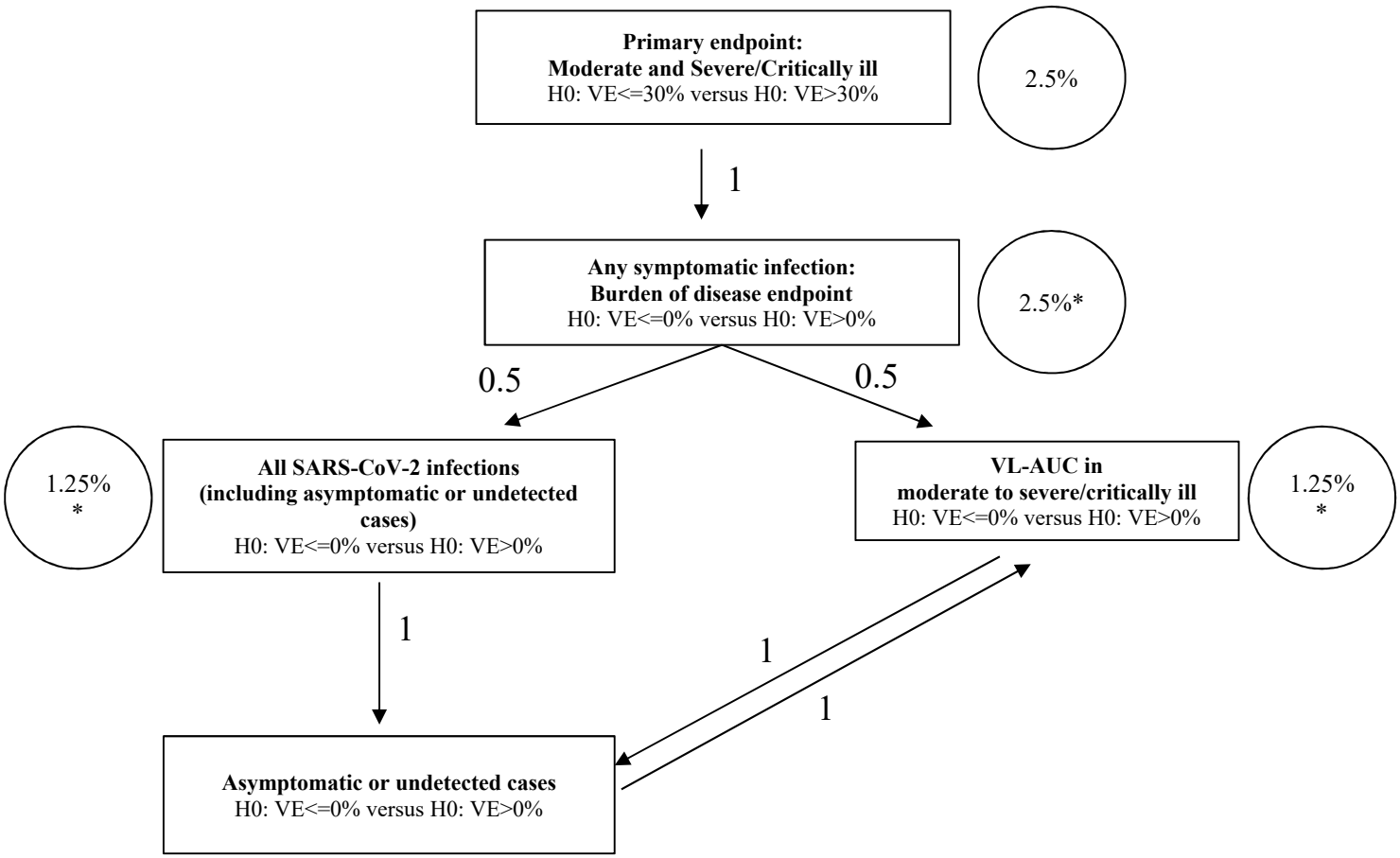
The evaluation of secondary endpoints will be adjusted for multiple testing of multiple endpoints (using graphical approach) and potential stopping at interim analysis evaluation using Pocock boundary (as suggested e.g. in Glimm, Maurer and Bretz, 2010).

The order of evaluation of multiple endpoints will be done according to the graphical method that is detailed below in Figure 2.

To adjust for the interim monitoring, a Pocock error-spending function will be employed: the information fraction to derive the appropriate alpha-level for a given endpoint will be deducted from the information fraction of the primary endpoint: # of available primary endpoint cases at the time of data base cut off divided by 154.

With 154 primary endpoints, the alpha-level for the secondary hypothesis is therefore 0.025 (2.5%). With, e.g., 77 primary endpoints, the information fraction equals 0.5 and the first secondary hypothesis (any symptomatic infection: burden of disease) is then evaluated at the alpha-level 0.0155. If this test is significant, the smallest p-value for the hypothesis of Any infection and VL-AUC are compared against 0.0155/2 (0.775%). If significant, the remaining hypothesis will be compared against 0.0155 (1.55%). If not significant, it will be compared against 0.0155/2 (0.775%).

Figure 2: Graphical approach for the hypothesis evaluation



*Pocock-adjusted based on information fraction of the primary analysis

It is expected that the number of events related to the endpoint of COVID-19 requiring Medical intervention (see Section 5.1.3.4) is insufficient for a powered statistical evaluation of this hypothesis. To that end, the hypothesis of medical intervention will be tested in a subsequent analysis when more data is available.

3. SAMPLE SIZE DETERMINATION

3.1. Efficacy (Total Sample Size)

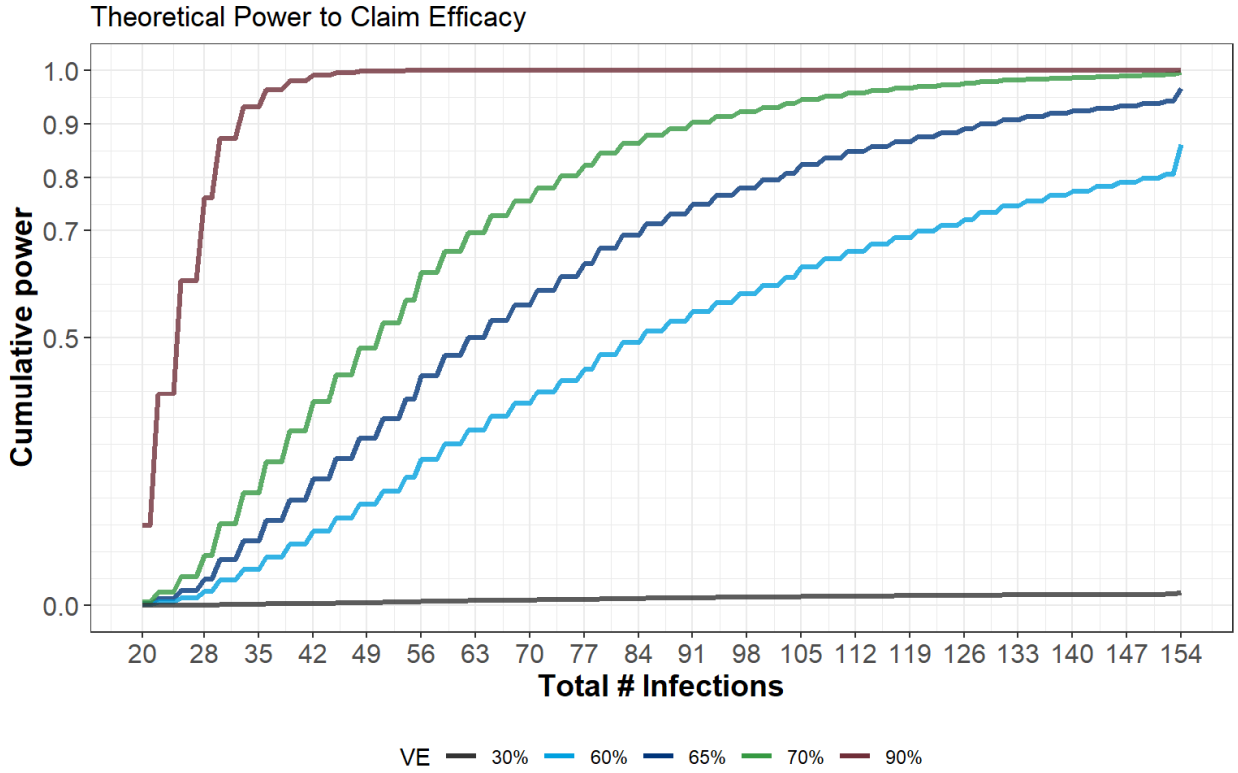
The study TNE is determined using the following assumptions:

1. a VE for molecularly confirmed, moderate to severe/critical SARS-CoV-2 infection of 60%.
2. approximately 90% power to reject a null hypothesis of H0: VE≤30%.
3. type 1 error rate α = 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 5.3.3.1).
4. 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 5.1.3 in the PP population at least 14 days after vaccination (Day 15) with study vaccine.

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 154, 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 5.1.3). Using the SPRT until the TNE when starting from the 20th endpoint onwards will result in 86.22% power to reject H0 when VE1=60%. The overall type I error is controlled below 2.5% at 2.398% when VE0=30%. In Figure 3 the power of the testing strategy for VE1 equal to 60%, 65%, 70% and 90% is shown for a total number of endpoints from 20 to 154. From the graph, the overall study power equals 96.6% for an assumed VE=65%, and close to 100% for an assumed VE=70%.

Figure 3 Theoretical Power based on the Exact Binomial distribution for VE1 = 60%,65%,70% and 90%; and Type I error rate under VE0 = 30%



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 is specified in section 2. The FWER will be controlled at 2.5%.

Sample Size Justification

Based on epidemiological modeling for the targeted study countries, province/states of the various site locations, the annualized incidence of moderate to severe/critical COVID-19 cases meeting the primary endpoint definitions has been predicted to be 1.4% for the October-November timeframe. The estimate incorporates that real-world-evidence data and literature data only detected and reported a fraction of SARS-CoV-2 infections.

Furthermore, it includes that, based on literature and real-world-evidence data, only a fraction of all infections meets the moderate and severe/critical COVID-19 case definition and the fraction varies by age as well (increasing with higher ages). Moreover, projections for the selected study regions indicate that incidences will decline over time. Finally, seroprevalence rates are expected to vary between 5-15%.

For the purpose of sample size evaluation, an incidence assumption of moderate to severe/critical COVID-19 cases meeting the primary endpoint definition of 1.4% during the first 3 months of the

study, with a 50% reduction in Month 4, and 62% reduction in the months thereafter is assumed in combination with a seroprevalence rate of 10%.

The epidemiological situation will remain uncertain during the course of the study: actual seroprevalence rates, degree of social distancing and use of personal protective equipment during the study, local regulations (eg, potential lockdowns, other vaccines if available) potentially becoming in effect during the course of the study and potential drop-outs from the study may impact the disease incidence rate.

To that end, the maximum sample size of approximately 60,000 participants will be selected. This sample size is selected, based on 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 8 months of the study for a vaccine with an assumed 60% VE.

Based on an estimated case-hospitalization ratio of 2.5% and estimates obtained from reported real-world-evidence data of 3-10% of all SARS-CoV-2 infections meeting the severe/critical COVID-19 definition, this will provide a reasonable likelihood of observing 5 severe cases in the placebo group within the same time frame (8 months).

3.2. Immunogenicity Subset

All participants included in the Immunogenicity Subset (N=400) will be added randomly at each stage of the staggered enrollment. Healthy adults (Subset 1a, n=100) will be enrolled in Stage 1a, adults with comorbidities (Subset 1b, n=100) in Stage 1b, healthy elderly (Subset 2a, n=100) in Stage 2a, and elderly with comorbidities (Subset 2b, n=100) in Stage 2b, with approximately 100 participants per group. The interactive web response system (IWRS) will be used to achieve these numbers and a 1:1 ratio between Ad26.COV2.S and placebo assignment within each Subset.

For 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 on Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year, 18 months, and 2 years after vaccination.

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

3.3. Immunogenicity Correlates (Correlates Subset)

Correlates will be assessed based on immune responses and transcriptome modifications measured in a random subcohort of vaccine recipients and in all vaccine recipients who experience a SARS-CoV-2 event (a primary endpoint or a secondary infection endpoint). Also, placebo participants will be included in this subset (placebo infected, seropositive [based on N-protein] non-infected and seronegative non-infected), if feasible. The goal of this case–cohort study is to assess correlates of risk of the primary endpoint and 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.

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

3.4. 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). Solicited AEs will be followed for 7 days, unsolicited AEs will be followed for 28 days.

3.5. Power calculations for other efficacy endpoints

3.5.1. Burden of disease endpoint

The statistical power associated with the BOD endpoint was evaluated under a range of scenarios for $VE_{\boldsymbol{mild}}$ and p_2 (the fraction of moderate/severe endpoints) with $VE_{mod/sev} = 70\%$ and $p_1 = 0.5$ (fraction of mild events). The power values for the null hypothesis of $VE = 0\%$ under the same scenarios were all equal to 100% for the BOD endpoint (not conditional on clearing the primary endpoint test and adjusted for multiplicity).

3.5.2. Asymptomatic infections and all infections (including asymptomatic)

According to epidemiological data (as of August 20, 2020), the cases in the placebo group were assumed to be distributed as follows: 45% asymptomatic cases, 25% mild infections, and 30% moderate/severe infections, according to the case definitions. Based on a VE as detailed in the table below, events were simulated according to a binomial distribution and the primary endpoints evaluated against the SPRT boundary.

Upon crossing the boundary, the power against asymptomatic or undetected infections as well as against the evaluation of all infections was calculated. The alpha level for that evaluation was adjusted according to the procedure detailed in the statistical hypothesis evaluation. A range of power-calculations has been provided, if AUC-VL is significant (and alpha can be transferred to the endpoint 'all infections') or if AUC-VL is not significant (and alpha cannot be transferred to the endpoint all infections).

The results are based on 1000 simulations. The powers presented are not conditional on passing the first 2 hypotheses.

Vaccine efficacy				Power		
All infections	**Moderate /Severe**	**Mild**	**Asymptomatic**	**Moderate/Severe**	**Asymptomatic**	**All infections**
50%	70%	60%	31%	96%	18% - 25%	98-99%
60%	70%	60%	53%	96%	62% - 71%	100%
40%	70%	60%	9%	96%	2-3%	83-89%

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Vaccine assignment will be analyzed according to an as-treated principle. The analysis sets that are used for the various analyses are described in Table 2.

Table 2: Analysis Sets

Analysis Sets	Description
Enrolled	The enrolled analysis set includes all participants who signed the ICF and who were not screen failures
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	All randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment.
Per Protocol Efficacy Set (PP; primary efficacy analysis set for vaccination studies)	Participants in the FAS who received study vaccine and who were seronegative at the time of vaccination and who have no major protocol deviations that were judged to possibly impact the efficacy of the vaccine. See below for a definition.
Per Protocol Immunogenicity Analysis Set (PPI)	All randomized and vaccinated participants, including those who are part of the Immuno 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 Immuno 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.

For the PP the following additional criteria will be applied:

- having received the vaccine according to the randomization schedule
- having received at least 80% of the scheduled vaccination volume (according to the administration log)
- met inclusion criteria 1 (informed consent was obtained)

Some violations will not lead to exclusion of the subject from the PP, but data from the time-point of major protocol deviation onwards will be excluded from the analysis (if all data post-vaccination is excluded, the participant will be excluded from the PP):

- use of prohibited concomitant medications or medical conditions that were judged to probably impact the efficacy of the vaccine based on blinded medical review will be assessed on a case by case basis and documented before confirming a case for continuous monitoring or data base lock
- administration of another SARS-CoV-2 vaccine before or during the trial
- the participant became aware of the treatment code.

The following variables are relevant for in/exclusion of analyses:

- Seropositive or seronegative at baseline. A baseline serologic test for past or current infection with SARS-CoV-2 will be performed for all participants. Samples for the baseline serologic tests will be sent to the central lab for testing. Results will be categorized as positive or negative. In case the test result is missing or unknown the participant will be excluded from analyses on seronegative participants.
- PCR positive (PCR+) or negative (PCR-) at baseline: a sample for SARS-CoV-2 infection at baseline will be collected for each participant. For participants with a positive SARS-CoV-2 infection during the study this sample will be tested. If a participant was PCR+ at baseline, the participant will be excluded from the PP set. A missing value will be considered as PCR- for analysis purposes.

Timing of the infection: the onset of a symptomatic SARS-CoV-2 infection is defined in section 5.1.3. Based on the onset of infection, subjects will be included as

- For analysis with onset after vaccination: if onset occurred on or after Day 2 in the study (i.e. the Day after vaccination or beyond). At this stage there is however no expectation that the vaccination has achieved its full efficacy.
- For analysis with onset 14 days after vaccination: if onset occurred at or after Day 15. Cases with an onset prior or at Day 14 will be excluded from the analysis.
- For analysis with onset 28 days after vaccination: if the onset occurred on Day 29 or beyond. Cases with an onset prior or at Day 28 will be excluded from the analysis.

Analyses of safety will be performed on the FAS.

Analyses of efficacy will be performed on the PP population and will be repeated on the FAS.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless otherwise indicated, all analyses will pool data across ages and with/without co-morbidities for evaluation without stratification.

Analysis adjusting for randomization factors will be explicitly mentioned when done and will include the age groups and with/without co-morbidities only.

Stratification for (mobile) site unit at the time of randomization was done to ensure balance in exposure to SARS-CoV-2 between randomized groups over time because of the spatiotemporal evolution of the epidemic. However, including all stratification factors (age by comorbidity by (mobile) site) in the analysis will result in a large number of 'empty strata' (i.e. without cases) as the TNE of 154 is substantially lower than the anticipated number of stratification levels. Therefore no summaries will be provided by this stratification factor (mobile unit).

5.1.1. Study Phases

A baseline (or reference) value will be defined as the value of the last available assessment prior to the vaccination on Day 1.

The safety analysis will present all results by study phase (see Section 5.1.2). Immunogenicity results will be presented per scheduled time point as appropriate. Listings will be shown per phase and time point.

Study day or relative day is defined as follows:

- Study Day = visit date – date of Day 1 + 1; if visit date >= date of Day 1 (date of first vaccination).
- Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of first vaccination).

5.1.2. Phase Definitions

The phases in the study will be constructed as follows:

Table 3: Phase Definitions for Safety Analysis

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
Post-dose	2	Post-dose	1	Date and time of first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days)
Treatment	3	Treatment	2	Day 15, 00:00	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) One minute prior to week 52 visit
Long term Follow-up	4	Long term Follow-up	3	Week 52 Visit	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) 23:59 at the date of last visit d) (a)

5.1.3. COVID-19 case classification

Definitions relevant to COVID-19 case classification are listed below.

- **Episode** (of COVID-19): An episode of COVID-19 is defined as the period of the onset of (COVID-19) symptoms up until resolution of the episode. The severity of a COVID-19 will be determined based on the maximum severity observed across the episode.

- **Onset of (**COVID-19) **symptoms:** This is the date when any sign(s) or symptom(s) suggesting possible COVID-19 was entered in the eCOA system. It will be called Day 1 of an episode. In case the eCOA system was not used to note the symptoms and onset, it is the date the first symptom of an episode was entered on the CRF by the site ("*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).*" CTP). [Day 1 will be derived based on the first symptoms that are entered in the eCOA before the first swab is taken. In case there are multiple days with symptoms entered in the eCOA before the first swab, Day 1 is defined as the first Day of all consecutive Days with signs or symptom that are at least mild.]

- **Resolution of an episode:** 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. [The date taken will be the first of the 2 consecutive negative

swabs, OR the first day with no COVID-19 related signs or symptoms, whichever comes last. For this determination, all sources of information will be used (eCOA, eCRF). In case of missing days, it will depend if those are before or after the first day of the two consecutive SARS-CoV-2 negative nasal swabs. If before days with missing data have no consequence. If after, it is assumed that if days with missing data are after a day with no symptoms, the subsequent days also were without symptoms. If days with missing data are after a Day with symptoms, the assumption depends on the data of subsequent Days. If there are no more than 2 Days without data and the next Day does have (at least mild) symptoms, the missing days will be assumed to also have had symptoms. In all other cases it will be assumed that days with missing data were without symptoms and the rule to determine the resolution of symptoms will be applied.]

- **Molecularly confirmed case:** Events for which a central SARS-CoV-2 PCR positive test was obtained.

- **Analysis-ready** case: A case is considered *analysis-ready* if it has a central SARS-CoV-2 positive test AND has reached the Episode Day 15 (i.e., 14 Days after onset). At this time it will be categorized as mild, moderate, severe/critical; and categorized according to the harmonized FDA definition (yes/no). Cases that have not resolved at or before Episode Day 15, will be categorized to the highest severity level reached at Episode Day 15. Statistical analysis against the monitoring boundaries will be performed on analysis-ready cases only (see Section 5.1.3).

- Case **not analysis-ready:** A case for which a SARS-CoV-2 test is positive, but the case has not reached Episode Day 15 yet; categorization is *not considered analysis-ready*. The SSG will be provided and derive with all analysis-ready and not analysis-ready cases (see Section 5.1.3). As the false-negative rate is low, for these cases also local SARS-CoV-2 PCR tests will be considered for cases not analysis-ready (but not for analysis-ready cases).

5.1.3.1. Assigning Case Definition

The case definitions for mild, moderate, and severe/critical COVID-19 are provided in the CTP Section 8.1.2. This section provides guidance on how these will be applied.

- Information on symptoms is to be collected from the eCOA (see Appendix 6 of the CTP) and from the eCRF entered by the site. In case the sources are inconsistent (i.e., on a single calendar Day one source records the symptom and another source does not record that same symptom) the symptom is considered to have been present on that Day.
- A sign or symptom is considered as absent or present for a COVID-19 episode: any sign or symptom is considered present if observed in the eCOA or eCRF for the COVID-19 episode, and absent if not.
- Signs or symptoms occurring at any time during the episode are used for the application of the case definitions.
- The application of the criteria is independent of duration; if a sign or symptom is present at any time, the sign or symptom is considered to be present. [Note that for a suspected

COVID-19 case to be tested, at least one symptom of suspected COVID-19 has to be present for 24 hours, and not otherwise explained (Section 8.1.1. of the CTP: "New onset or worsening of any 1 of these symptoms, which lasts for at least 24 hours, not otherwise explained"). For case classification the information from the eCOA and eCRF is taken independent of duration or alternative explanations.]

- Fever will be assessed independent of method (oral, armpit, ear, or rectal).
- The definitions of *mild*, *moderate*, and *severe/critical* are mutually exclusive, where the most severe category takes priority.
- At the time of resolution of the COVID-19 episode, the collected information will be applied against the clinical case definition. For the purpose of continuous monitoring, the clinical case definition will be considered as analysis-ready at Day 15 independent of resolution (see above). In case symptoms worsen after Day 15, increasing the classification of severity, the next continuous monitoring analysis will analyze the case according to the highest degree of severity at that time (see Section 5.8).

For any case definition to be considered for classification of COVID-19 there needs to be at least one 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) that is confirmed by the central laboratory.

As there can be specific unforeseen situations where definitions as detailed in the SAP did not cover the specific situation, the Sponsor will at that time define additional data handling guidelines based on an assessment (blinded to treatment assignment) as close as possible to the intent of the rules as specified above. The Study Statistics and Programming team at the Sponsor will provide their additional data handling guideline to the SSG, which will be documented in the Data Presentation Specification document (DPS).

5.1.3.2. Symptomatic COVID-19 Case Derivation

Some symptoms lead to suspicion of a COVID-19 and are used as triggers to proceed with home-collection of the nasal swabs for SARS-CoV-2 testing as based on interaction of the participant with the site. The list of symptoms used as triggers for testing are provided in Section 8.1.1. of the CTP. A triggering symptom may lead to a (confirmed) positive SARS-CoV-2 test, where the case may fail to reach the mild case definition (or worse) at any time during the episode. These cases are not considered as symptomatic. In other words, symptomatic COVID-19 cases are those that are at least of mild severity as defined below.

Asymptomatic cases are defined as cases where a participant does not fulfil the criteria for mild, moderate or severe/critical COVID-19, and has a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample, OR develops a positive serology (non-S protein) test. In those cases the participant will be considered to have experienced asymptomatic or undetected COVID-19.

5.1.3.3. Mild COVID-19 Case Derivation

A case will be considered of mild COVID-19 severity if one (or more) of the following symptoms is observed, if not satisfying the definition of a moderate or severe/critical disease severity [black, terminology from eCOA or blue, terminology from the eCRF]:

- Fever (≥38.0°C or ≥100.4°F) or eCRF
- Sore throat / Sore throat
- Loss of appetite / Malaise
- Feeling generally unwell (run down) / Malaise
- Fatigue (tiredness) / Malaise
- Physical Weakness] / Malaise
- Headache / Headache
- Muscle aches/pains / Myalgia
- Diarrhea / Gastrointestinal Symptoms
- Vomiting / Gastrointestinal Symptoms
- Nausea / Gastrointestinal Symptoms
- Abdominal/stomach pain / Gastrointestinal Symptoms
- Cough / Cough
- Chest congestion (mucus in chest)
- Runny nose
- Wheezing
- Skin rash
- Eye irritation/discharge
- Chills
- Uncontrollable body shaking/shivering
- Decreased sense of smell / Anosmia (olfactory or taste disorders)
- Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Red or bruised looking feet or toes / Chilblains/pernio (red or bruised looking feet or toes)

5.1.3.4. Moderate COVID-19 Case Derivation

For the definition of moderate COVID-19 severity there are two separate criteria, either if met would be sufficient to be considered as moderate (if not satisfying the criteria of severe/critical disease):

1. At least one **sign** or symptom (as derived from the Medically-attended COVID-19 Form (MA-COV) form or other CRF source *or eCOA*):

- Respiratory Rate ≥ 20 breaths/minute or vital signs CRF
- Abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level
- Clinical or radiologic evidence of pneumonia
- Radiologic evidence of DVT
- *Shortness of breath (difficulty breathing)*

OR

2. Two (or more) signs or symptoms from of the following (black, terminology from eCOA or blue, terminology from the eCRF):

- Highest temperature was ≥38.0 ºC or ≥100.4 ºF or CRF
- Heart rate ≥ 90 beats/minute or vital signs CRF
- Chills
- Uncontrollable body shaking/shivering
- Sore throat / Sore throat
- Cough / Cough
- At least one from [Loss of appetite, Feeling generally unwell (run down), Fatigue (tiredness), Physical Weakness] / Malaise
- Headache / Headache
- Muscle aches/pains / Myalgia
- At least one from [Diarrhea, Vomiting, Nausea, Abdominal/stomach pain] / Gastrointestinal Symptoms
- Decreased sense of smell or Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Red or bruised looking feet or toes / Chilblains/pernio (red or bruised looking feet or toes)

5.1.3.5. Severe/Critical COVID-19 Case Derivation

A case will be considered severe/critical if (black, terminology from the Medically-attended COVID-19 Form (MA-COV) or blue, terminology from the eCRF):

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg)

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- 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 (Medical Encounters eCRF)
- Death (SAE form)

5.1.3.6. US FDA Harmonized COVID-19 Case Derivation

A case will be considered satisfying the FDA harmonized COVID-19 case criteria if at least one of the following symptoms was recorded during a COVID-19 episode (black, terminology from eCOA or blue, terminology from the eCRF):

- Fever (≥38.0°C or ≥100.4°F) or CRF
- Cough / Cough
- Chills (or Uncontrollable body shaking/shivering)
- Sore throat / Sore throat
- Shortness of breath (difficulty breathing)
- Fatigue (tiredness) / Malaise
- Muscle aches/pains / Myalgia
- Headache / Headache
- Decreased sense of smell / Anosmia (olfactory or taste disorders)
- Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Sore throat / Sore throat
- Chest congestion (mucus in chest)
- Nasal congestion (stuffy nose)
- Runny nose
- Joint aches/pains
- Diarrhea / Gastrointestinal Symptoms
- Vomiting / Gastrointestinal Symptoms
- Nausea / Gastrointestinal Symptoms

The FDA harmonized COVID-19 case definition is independent of the case definition above, meaning that each subject with a case of molecularly confirmed COVID-19 is considered as an

FDA harmonized case (yes/no), and considered as either a case of mild, moderate, or severe/critical case.

5.2. Participant Dispositions

Participant information will be shown for the full analysis set.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- participants screened
- participants screen failed (and main reason for screen failure)
- participants in the FAS
- participants in the PP
- participants in the FAS but not in the PP (and reasons for not being in the PP)
- participants vaccinated and not randomized
- participants randomized and not vaccinated
- participants vaccinated with incorrect treatment
- participants who discontinued study (and reasons for termination)

Also, the number of participants and percentage per phase will be tabulated.

5.3. Primary Endpoint(s) Analysis

5.3.1. Timepoint of primary analysis

The interim monitoring for the primary analysis can start as soon as the following conditions are met:

1. The first 50% of planned participants i.e. after 30,000 subjects had at least 2 months of follow-up after vaccination
2. A minimum of 6 COVID-19 primary endpoint cases for the ≥60 years age group
3. At least 20 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19
4. A subset of at least 5 cases meeting the definition of 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 1-4 are met.

The primary analysis will be triggered by either:

a) An interim evaluation if both prespecified efficacy boundaries have been met OR if at least 154 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 are observed

AND

b) The above 4 conditions are met.

OR, alternatively,

If the prespecified non-efficacy has been met (evaluating events with start 14 days after vaccination) or when the harm boundary has been crossed. The decision rules for harm and non-efficacy are detailed in Section 5.8.

If more than 154 primary endpoints are observed before the 4 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.

5.3.2. Definition of Endpoint and Estimand

The primary endpoint is defined as a COVID-19 case meeting either the moderate or severe/critical case definition with onset 14 days post vaccination as defined in Sections 5.1.3.4 and 5.1.3.5.

The other estimand attributes therefore are:

Population: Prior SARS-CoV-2-uninfected, adults ≥18 years with or without comorbidities for COVID-19

Endpoint: Confirmed symptomatic moderate to severe/critical COVID-19 infections with onset ≥14 days after study vaccination, as defined in section 8.1.3.1 of the protocol.

Interventions: Ad26.COV.S2 5×10^{10} vp and placebo

Summary Measure: Vaccine Efficacy: 100 x (1-ratio of incidence vaccine/placebo)%

Intercurrent Events: None

Data handling for estimators: Subjects with major protocol deviations potentially impacting efficacy will be excluded from the analysis. Subjects with a positive serology test at baseline will be excluded from the analysis. Cases will be counted from Day 15 until and including the last available timepoint in the data base.

5.3.3. Analysis Methods

Vaccine efficacy and evaluation of the primary hypothesis will be done based on the truncated sequential probability ratio test (Section 5.3.3.1) in the per-protocol analysis set including seronegative subjects.

The pre-specified boundary to declare a significant result is based on a one-sided truncated SPRT, assuming approximately 90% power to detect a VE=60%, at a 2.5% one-sided significance, starting from the 20th COVID-19 case in the PP population that meets the primary endpoint definition, up and until the 154th case (value at which the testing is curtailed). The boundary is visualized in Figure .

In case interim monitoring has started (i.e. because minimal data requirements 1-4 were met) and the total number of events at the time of the primary analysis exceeds the TNE, e.g. due to rapid accrual of events in the last week, the SPRT boundary will be extended until the observed total number of events, keeping the overall alpha below 2.5% one-sided. This is achieved by avoiding the truncation of the SPRT boundary at the TNE, distributing the remaining alpha across the overrun events, in such a way as to maximize the boundary at the observed total number of events.

The operational evaluation of this boundary is detailed later in this section. As soon as this prespecified boundary has been crossed and the primary hypothesis of vaccine efficacy (VE) against moderate to severe infections the PP set: H_0: VE ≤30% versus H_1: VE >30% will be established.

Vaccine efficacy and the associated adjusted 100% (1-α*) - confidence interval will be estimated as referenced in Appendix 8.

To evaluate whether the second efficacy criterium has been met, the VE against severe infections will be calculated, as soon as the primary endpoints contain a subset of 5 severe events. If the point estimate VE >= 50% AND a minimum of 5 cases observed in the placebo group, this criterium is considered to be met.

The primary analysis will be supplemented with a subgroup analysis for age group (18 to <60 years, ≥60 years) and presence of comorbidities (yes/no) employing a descriptive summary including (unadjusted) 95% confidence intervals to describe the VE in each subpopulation using the same methods. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (≥70 years, ≥80 years). No hypothesis testing will be performed in these subgroups.

5.3.3.1. Sequential Probability Ratio Test

Using a similar notation of Dragalin et al. (2002) and Dragalin and Fedorov (2006) consider, X_1 and X_2 the number of events in the placebo group and the vaccine group, respectively. 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 $H1: \pi = \pi^*$using the conditional binomial test.

Consider $\alpha = P(reject\ H0|VE = VE_0)$ 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, the TNE 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. Under the assumptions stated in Section 3.1, this formula suggests a TNE of T^*=154.

The implemented critical boundaries for success (Section 5.8.5) are based on the truncated SPRT (cfr. Jennison and Turnbull, 2000, chapter 12) 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. These boundaries are created by comparing the Likelihood Ratio of observing X_2 out of T endpoints under $H1$ vs. $H0$, using the above-mentioned exact binomial distribution. If the log-likelihood ratio is larger or equal to $ln(1 - \beta)/\alpha$ then H1 is concluded.

5.3.4. Operational implementation of SPRT and analysis in case of overrun

Based on modeling and simulation to minimize the risk of inconsistency and operationally to increase consistency in case evaluation, the evaluation whether or not the efficacy boundary has been crossed will be done on at least a weekly basis.

The boundary will be evaluated based on the available cases i.e., a COVID-19 episode that has been molecularly confirmed and analysis-ready according to the severity scale. The COVID-19 may still be ongoing.

1. Every week, the available analysis-ready cases for efficacy monitoring will be evaluated against the primary endpoint definition and analysis population.

2. Based on the total number of analysis-ready cases and the vaccine:placebo ratio, the SSG will evaluate against the prespecified boundary whether the primary hypothesis has been rejected.

3. In case of rejection, the DSMB will provide the recommendation to proceed to the primary analysis to the Governance Committee upon which a decision can be implemented.

When the decision is reached to proceed to the primary analysis, the database cut-off date will be set to the date of the analysis when the boundary was crossed. The primary analysis will be based on the analysis at the time the boundary has been crossed and will be based on the cases of COVID-19 that were analysis-ready at this database cut-off date. The analysis of the secondary endpoints will include all analysis ready and resolved cases at the time of database lock.

Due to the 14 days evaluation of the severity of COVID-19 the database may include additional COVID-19 cases that were not analysis-ready at the database cut-off date. These cases will be listed, but will not be analyzed. The safety analysis, including SAEs, will use all data available at the time of database lock.

For the operating characteristics of the SPRT and the statistical considerations justifying the practical implementation, the reader is referred to the modeling and simulation report.

5.3.5. Supportive analyses

The primary analysis will be supplemented with the following analyses.

For subjects with molecularly confirmed COVID-19, the follow-up time is defined as the time between vaccination and the time of onset of the case. For all subjects without COVID-19, follow-up time is defined as the time since vaccination until the last available measurement (for subjects ongoing in the study) or study discontinuation/completion.

Time to first occurrence of molecularly confirmed moderate or severe/critically ill COVID-19 is defined as the time between vaccination until onset of the case. Subjects without moderate and severe/critically ill COVID-19 are censored at their follow-up time as defined above.

In a supportive analysis of the primary efficacy endpoint, vaccine efficacy will be estimated with an associated two-sided confidence interval (Wald test) based on the hazard ratio obtained from a Cox proportional hazards regression model. The analysis will be stratified for age (>=60 yrs, <60 yrs) and comorbidities (with or without comorbidities). The alpha-level at the time of crossing the boundary will be used to calculate the confidence interval.

The primary and supportive analysis as described for moderate and severe/critically ill COVID-19 cases in the per-protocol population in seronegative subjects will be repeated using the following analysis populations and endpoints:

- FAS, SN (seronegative) with onset of molecularly confirmed, moderate and severe/critically ill COVID-19 one day after vaccination
- PP, SN with onset of molecularly confirmed, moderate and severe/critically ill COVID-19 with onset 28 days after vaccination

The primary efficacy analysis will be repeated regardless of serostatus, if > 6 moderate and severe/critically ill COVID-19 observed in seropositive subjects.

5.3.6. Sensitivity analyses

In case of potential waning VE over time the cumulative incidence vaccine efficacy against moderate or severe/critical COVID-19 with onset 14 days post vaccination will be evaluated in the PP set, where all participants were seronegative at the time of vaccination. The method of Zeng (2004) will be used to estimate the cumulative incidence functions within each intervention arm, and pointwise two-sided Wald-based 95% confidence intervals for a log-transformed cumulative incidence ratio estimate will be provided over time. These intervals will be transformed to yield intervals for the cumulative incidence VE.

To evaluate the sensitivity to potential differential exclusion of major per-protocol deviations in the primary estimand, the following causal inference methods may be used. The efficacy will be estimated marginally among all participants who were seronegative at the time of vaccination in

the full analysis set (FAS-SN). Longitudinal causal inference methods will be used to formally define this efficacy estimand. In particular, having major protocol deviations will be treated as a time-varying intervention and the estimand is defined as efficacy in the counterfactual world where no participants have a major protocol deviation and no participants are lost to follow-up (Robins, 1986). Methods for estimating this quantity make use of data from all participants in the FAS-SN cohort, including those who, in fact, do not belong to the PP set. For the causal estimand to be learnable from the data available, these methods require that time-varying covariates are available such that, at any given time, whether or not a person has yet had a major protocol deviation or has been lost to follow-up is independent of whether or not the person would have subsequently experienced moderate to severe COVID-19 in the scenario where, possibly contrary to fact, that person had not yet had a major protocol deviation or been lost to follow-up. Covariates to be considered include demographics, clinical participant characteristics, and clinic-level information.

A sequentially doubly robust targeted minimum loss-based estimator (TMLE) will be used to estimate the aforementioned causal efficacy estimand (see Algorithm 1 in Luedtke, 2017; see also van der Laan and Gruber, 2012). This TMLE has been shown to be more robust than alternative methods for estimating longitudinal causal effects (e.g., Bang and Robins, 2005 and van der Laan and Gruber, 2012). The TMLE that we will use is designed for a setting where time is discrete, and its performance guarantees rely on the number of time points not being too large relative to the sample size. Therefore, to properly account for the fact that moderate to severe COVID-19 is measured on a daily scale, the TMLE will be run with time discretized into two-week windows, and then the fact that events are measured on a finer scale will be accounted for by incorporating inverse probability of censoring weights into the estimation procedure.

The resulting TMLE requires an estimate of the probability of experiencing moderate and or severe COVID-19 by the start of each two-week period considered, conditionally on time-varying covariates and intervention arm. Similarly, the TMLE also requires the probability experiencing a composite censoring event by the start of each of these two-week periods, conditionally on these same variables, where this composite censoring event is defined as either having a major protocol deviation or being lost to follow-up. Both of these estimates will be obtained using the ensemble method superlearner (van der Laan, Polley, and Hubbard 2007) with logistic regression, using the cross-entropy loss function and 5-fold cross-validation. Superlearner selects an optimal weighted combination of the predictions from a collection of candidate regression algorithms, such as those based on generalized linear models or random forests. Each superlearner will be supplied with the following library of learners: SL.mean, SL.step, SL.bayesglm, SL.glm, SL.glm.interaction, SL.glmnet, SL.earth, SL.xgboost, SL.ranger. Inverse probability of censoring weights will be obtained using a Kaplan-Meier estimator for the time to the composite censoring event, conditionally on being at risk at the beginning of the given two-week window. A 95%-level Wald-type confidence interval will be developed for the log-transformed cumulative incidence ratio, and will then be transformed to yield a confidence interval for the vaccine efficacy.

5.3.7. Tabulations and Graphical displays

The time to onset of the first occurrence of molecularly confirmed COVID-19 (definition in section **Error! Reference source not found.**) will be graphically summarized using Kaplan-Meier m ethods for the following subgroups:

For moderate or severe/critical COVID-19,

- PP, seronegative subjects only with onset 14 days after vaccination
- PP, seronegative and seropositive subjects with onset 14 days after vaccination
- FAS, seronegative subjects only with onset 1 day after vaccination
- FAS, seronegative and seropositive subjects with onset 1 day after vaccination

These graphs will be summarized for each type of infection separately as well (moderate or severe/critically ill COVID-19).

Furthermore, the number of events and incidence for each endpoint and population (#of events/#person-years of follow-up) will be tabulated by randomized group. For the tabulations regardless of serostatus, cases will be additionally summarized by serostatus at baseline and combined.

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%] with the method of Parzen, Wei and Ying applied to estimate pointwise and simultaneous $(1-\alpha)\times 100\%$ CIs.

Any subgroup analysis for VE will also be visualized with forest plots.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Tabulations and graphical displays

The time to onset of the first occurrence of molecularly confirmed COVID-19 will be graphically summarized using Kaplan-Meier methods for the following analysis populations following subgroups:

- PP, baseline-seronegative subjects only with onset 14 days after vaccination
- PP, baseline-seronegative and baseline-seropositive subjects with onset 14 days after vaccination
- FAS, baseline-seronegative subjects only with onset 1 day after vaccination
- FAS, baseline-seronegative and baseline-seropositive subjects with onset 1 day after vaccination

These graphs will be prepared regardless of severity according to the case definitions mild, moderate and severe and for the US FDA harmonized case definition. Furthermore, the graph will be prepared by severity (for mild COVID-19 only, COVID-19 requiring medical intervention).

The number of events and event rate for each endpoint and population (#of events/#person-years of follow-up) will be tabulated by randomized group.

Unless otherwise indicated, follow-up time for each subject is defined as time since vaccination until onset of a COVID-19 episode or the last available study measurement (For subjects without a COVID-19 episode).

Any subgroup analysis for VE will be visualized as well with forest plots.

5.4.2. Key Confirmatory Secondary Endpoint(s) and Estimand(s)

5.4.2.1. Definition of Endpoint(s)

Endpoint Label	Endpoint definition
Any symptomatic infection (BOD)	For all subjects with a symptomatic, molecularly confirmed COVID-19 episode, classification based on any severity will be included. Weight-adjusted analysis for severe disease will be done as follows. Any case of mild or moderate COVID-19 will be given a score of 1, severe/critical COVID-19 cases will be given a score of 2. Subjects without a symptomatic, molecularly confirmed COVID-19 episode are implicitly categorized as 0.
Asymptomatic or undetected infection	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. Serologic conversion at the time of the primary analysis is based on the available data from Month 2.5, Month 6 or Month 12. If positive at any timepoint while the subject was seronegative at baseline, a subject is considered seroconverted.
All infections	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset after vaccination with study vaccine.

COVID-19 requiring Medical intervention	First occurrence of COVID-19 requiring medical intervention defined a requiring: Hospitalization ICU admission mechanical ventilation ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) or linked to any molecularly confirmed, COVID-19 during a COVID-19 episode.
Viral Load AUC (VL-AUC)	Area under the viral load-time curve (VL-AUC in log_{10} copies/ml) of SARS-CoV-2 viral RNA load as determined by quantitative RT-PCR assay of nasal available samples during the COVID-19 episode. Nasal swab samples are taken at the start of the COVID-19 episode and every 2 days thereafter for the next 14 days or until 2 consecutive negative swabs, whichever occurs later. VL-AUC is calculated based on the viral load values until resolution of the COVID-19 episode. This will be calculated for all subjects with a moderate or severe/critically ill endpoint. In the calculation of the AUC, all available information (date, timing in hours, and minutes as captured in the data base will be used, but the AUC result will be reported in hours), of the assessment, is taken into account. Data handling regarding the following will be added to the Data Presentation Specifications (DPS): • PCR local lab versus central lab data • saliva • handling of values below LLOQ/LLOD $$\boldsymbol{AUC\ VL = \sum_{i=2}^{T} \frac{[VL_{t_i} + VL_{t_{(i-1)}}]}{2} [t_i - t_{(i-1)}]}$$ where $t_i = (actual)\ timepoint\ i$ $t_{i-1} = (actual)\ timepoint\ (i-1)$ $T = last\ timepoint$ $t_1 = first\ timepoint$ $VL_{t_i} = log_{10}\ viral\ load\ at\ \ (actual)\ timepoint\ i$

	$VL_{t_{(i-1)}} = log_{10}\ viral\ load\ at\ \ (actual)\ timepoint\ (i-1)$ This will be calculated for all subjects with a molecularly confirmed infection.

The confirmatory estimands therefore are

Population: Prior SARS-CoV-2-uninfected, adults ≥18 years with or without comorbidities for COVID-19

Endpoint: as defined above.

Interventions: Ad26.COV.S2 $5x10^{10}$ virus particles and placebo

Summary Measure: Vaccine Efficacy: 100x(1-ratio of endpoint mean vaccine/placebo)%

Intercurrent Events: /

Data handling for estimator: Subjects with major protocol deviations potentially impacting efficacy will be excluded from the analysis. Subjects with a positive serology test at baseline will be excluded from the analysis.

For the secondary endpoints all available cases at the time of data base cut off will be included in the analysis according to the pre-specified analysis population and time window for endpoint calculation.

The populations for analysis for the secondary endpoints are:

Table 4 Key confirmatory secondary endpoints and analysis set evaluations

	Key analysis population for evaluation of the statistical hypothesis	**Supportive analysis set**
Any symptomatic infection (BOD)	Per-Protocol analysis set baseline-Sero-Negative subjects with onset of infection 14 days post vaccination	PP, SN, Day 14 PP, SN/SP, Day 14* FAS, SN, Day 1 PP, SN, Day 28
Any infection	Full analysis set Sero-Negative subjects with onset of infection 1 day post vaccination	FAS, SN/SP, Day 1*
Medical intervention	Per-Protocol analysis set Sero-Negative subjects with onset of infection 14 days post vaccination	PP, SN, Day 14 PP, SN/SP, Day 14* FAS, SN, Day 1 FAS, SN/SP, Day 1*
Viral Load AUC	Per-Protocol analysis set Sero-Negative subjects with onset of infection 14 days post vaccination	PP, SN, Day 14 PP, SN/SP, Day 14* FAS, SN, Day 1 FAS, SN/SP, Day 1*

Asymptomatic or undetected infection	Full analysis set Sero-Negative subjects with onset of infection 1 day post vaccination	FAS, SN/SP, Day 1*
PP=per-protocol, SN=sero-negative subjects, Day 1/14=including infections with onset 1 day/14 days post vaccination, SP=seropositive subjects, FAS=full analysis set (*)Any analysis regardless of serostatus will be done only if 7 or more events observed in the group of subjects who were seropositive at baseline.		

5.4.3. Supportive Secondary Endpoint(s)

To understand and characterize the vaccine efficacy against any symptomatic infection, as well as under any infection, the following supportive endpoints will be supplemented with the confirmatory secondary endpoints.

The evaluation of secondary endpoints will be done in the per-protocol analysis set in seronegative subjects, with onset 14 days after vaccination. All analyses will be repeated regardless of serostatus.

	Endpoint definition
Mild infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting mild definition with onset 14 days post vaccination.
Moderate infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting moderate definition with onset 14 days post vaccination.
Severe/critical infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting severe/critical definition with onset 14 days post vaccination.
US FDA Harmonized COVID-19 cases	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting the US FDA harmonized case definition with onset 14 days post vaccination

5.4.4. Analysis Methods

5.4.4.1. VE against any symptomatic infection – burden of disease

To evaluate the vaccine efficacy against any symptomatic infection, the severity-adjusted vaccine efficacy VE_{BOD} will be calculated based on BOD as follows. This vaccine efficacy measure is equal to the percent reduction in mean BOD score in the vaccine arm relative to that in the placebo arm.

Letting p_1 and p_2 denote, respectively the relative incidence of mild and moderate infections among symptomatic infections, and VE_1, VE_2, VE_3 represent, respectively, the vaccine efficacy for mild, moderate and severe/critical infections, the vaccine efficacy for BOD, under 1:1 allocation for vaccine and placebo, can be expressed as

$$VE_{BOD} = 1 - \left[(1 - VE_1)p_1 + (1 - VE_2)p_2 + 2(1 - VE_3)\big(1 - (p_1 + p_2)\big)\right] / \big(2 - (p_1 + p_2)\big)$$

Letting $BOD_V(n)$ and $BOD_P(n)$ represent the sums of the BOD scores for (symptomatic) infections in the vaccinated and placebo arms, respectively, then the estimated vaccine efficacy for the BOD endpoint after n infections (under equal allocation to vaccine and placebo) is $\widehat{VE}_{BOD}(n) = 1 - BOD_V(n)/BOD_P(n)$. An expression for an (asymptotic) lower confidence bound for VE_{BOD} based on $\widehat{VE}_{BOD}(n)$ is provided in (supplementary appendix, Mehrotra et al, 2020). The alpha* - level of the confidence interval will be compared against 0.

This lower bound will be compared against 0% to evaluate the study hypothesis against any symptomatic infection according to the statistical testing strategy specified in section 2.

In addition, the vaccine efficacy will be estimated with an associated unadjusted confidence interval for each severity separately (mild, moderate, severe/critical) according to the case definition.

Estimators for VE1, VE2 and VE3 in the PP-SN, together with their 95% CIs, are presented in appendix 8.

5.4.4.2. All infections and asymptomatic infections

The proportion of subjects (out of subjects with available measurements) who serologically converted will be graphically visualized and tabulated at every available timepoint by randomized group, together with the number of subjects with an available measurement.

Additional tabulation will summarize the number of subjects with and without a SARS-CoV-2 infection as having

1. Not infected
2. Asymptomatic or undetected subjects
3. Molecularly confirmed SARS-CoV-2 infection without any classification to mild, moderate or severe case definition (non-classified COVID-19)
4. Symptomatic molecularly confirmed, with mild COVID-19
5. Symptomatic molecularly confirmed, with moderate COVID-19
6. Symptomatic molecularly confirmed, with severe COVID-19

A subject will be classified based on their worst occurrence and in one category only.

All subjects with multiple SARS-CoV-2 molecularly confirmed infections during the study will be tabulated by severity and vaccination group in the FAS-SN/SP set.

To assess the effect of Ad26.COV2.S on occurrence of any infection with SARS-CoV-2 as compared to placebo, VE will be estimated with an associated adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as

detailed in section. To evaluate the hypothesis H0: VE<=0, the lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of protection against infection will be rejected.

To understand the vaccine efficacy evaluating asymptomatic infections, this analysis will be subsequently be followed with the effect of Ad26.COV2.S on occurrence of asymptomatic or undetected infections with SARS-CoV-2 alone, as compared to placebo. To that end, the VE will be estimated with an associated adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0, the lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of protection against infection will be rejected.

For cases, the follow-up time is defined as the time between vaccination and the time of onset of infection (timepoint of a positive N-protein Elisa for asymptomatic subjects).

5.4.4.3. Medical intervention

At the primary analysis the vaccine efficacy will be summarized with a 95% confidence interval (methods in Appendix 8)

For cases, the follow-up time is defined as the time between vaccination and the onset of the first event (according to the considered endpoint), for non-cases, it is the time between vaccination and data base cut off date (for subjects ongoing) or study discontinuation.

5.4.4.4. AUC viral load

To compare VL-AUC after infection between the active and placebo groups, the exact Wilcoxon Rank Sum test will be performed. Its one-sided p-value will be interpreted at the significance level determined in accordance with the multiple hypothesis testing strategy devised in section 2 based on all subjects who experience moderate or severe/critical COVID-19 in the per protocol analysis set with onset of infection occurring at least 14 days post randomization.

For the primary analysis, values below the LLOQ (indicated as 'Not Quantifiable' in the data base) will be imputed with 0. At the time of the final analysis, the same analysis will be repeated, so values below the LLOQ (indicated as 'Detected' or 'Not Detected') will be imputed with 0.

These imputations will be used when calculating the AUC based on equation (1). In addition, in case some observations are missing at the first timepoint after infection and/ or the last timepoint after challenge, missing values should be imputed with 0. No other missing values will be imputed.

AUC-VL values will be descriptively summarized (mean, median, SD, SE, range) by randomized group and COVID-19 severity. Individual profiles of viral load over time and log10[viral load] over time since onset of a COVID-19 episode will be summarized by randomized group and severity of COVID-19.

The vaccine efficacy against AUC-VL will be estimated through the geometric mean ratio of AUC-VL with associated 95% confidence interval.

As the comparison of the AUC VL after infection between the active and placebo groups is based on post-randomization groups, this analysis may not assess the causal effect of the vaccine on viral load. A sensitivity analysis as described by Gilbert et al. (2003) will be carried out. In this sensitivity analysis, a logistic selection bias model is employed to define a causal estimator for the vaccine effect on viral load. The unknow slope (b) of this logistic model determines the amount of selection bias; b is varied over a plausible range of values. For each value of b, a non-parametric estimate of the causal vaccine effect is calculated. A confidence interval and p-values for the appropriate hypothesis of interest are obtained by bootstrap. If b<0, there is a selection bias towards a lower viral load in the vaccine group as compared to the placebo group. When b=0, no selection bias is assumed. The hypothesis of interest is the one-sided hypothesis of a reduction of the viral load. Therefore, values of b ≤0 will be considered (from -5 to 0 in steps of 0.01). The estimate of the causal vaccine effect with its 100*(1-alpha/2) % confidence interval and the p-value for the one-sided hypothesis of a viral load reduction in the vaccine group will be plotted against the assumed value of b. The choice of alpha will depend on the outcome of the sequential testing procedure.

The analysis will be carried using R-code developed by P.N. Gilbert and R.J. Bosch. Number of bootstrap samples will be set to 10000 to achieve adequate precision for the derived p-values. The seed will be fixed to allow reproducibility of the result.

5.4.4.5. US FDA Harmonized definition

Estimating the Vaccine Efficacy (*VE*) and the associated confidence interval for the US FDA harmonized definition will be done according to the methodology as explained in Appendix 8.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

The potential association between vaccine efficacy and baseline or other potential influential factors (including but not limited to region, age group, comorbidities, Ad26 VNA seropositivity, SARS-CoV-2 seropositivity, profession, smoking status, seropositivity against other coronaviruses and coinfection with any other respiratory pathogens and other risk factors) will be explored by multivariate, covariate-adjusted analyses or subgroup summaries.

All exploratory endpoints analysis will occur in the PP analysis set, in seronegative subjects unless otherwise indicated.

Other ad hoc analyses may be performed if deemed appropriate to characterize the safety, immunogenicity and efficacy profile of the vaccine. Post-hoc analyses (analyses performed that are different from this SAP) that are included in the final CSR will be documented in the Changes to Planned Analyses section of the CSR.

5.5.1.1. Definition of Endpoint(s)

Endpoint	Endpoint definition

Time to SARS-CoV-2 virus no longer detectable	A subject is considered as having an infection if the case is classified as mild, moderate or severe. For each subject the time to "SARS-CoV-2 virus no longer detectable" is the time between the onset of the COVID-19 episode and the first sample that is negative and after which no positive sample was observed. For this assessment only centrally confirmed assessments will be taken into account. The precision of this difference will be in Days, defined as the Day of the episode where this criterion is met (e.g., if the first sample that was negative was on Day 12 of the episode, the time to no longer detectable will be set at 12 Days.
Peak viral load	A subject is considered as having an infection if the case is classified as mild, moderate or severe. The peak viral load is defined as the highest viral load that was observed during a COVID-19 episode. For this assessment only centrally confirmed assessments will be taken into account.
Viral load over time	A subject is considered as having an infection if the case is classified as mild, moderate or severe. For this assessment only centrally confirmed assessments will be taken into account. For each assessment the viral load will be categorized to the two day schedule, where the first value will define the series. If a viral load is available before and after a scheduled day, the average on the $\log_{10}$ scale will be used. If only one value is available in an adjacent day this value will be used.

The additional endpoints on viral load by quantitative RT-PCR are defined above, and will be analyzed descriptively for moderate to severe/critical cases and for all symptomatic cases separately (cases of mild COVID-19 or worse).

Assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed, mild COVID-19 by serial viral load measurements during the course of a COVID-19 episode.

First occurrence of any health care utilization linked to any molecularly confirmed COVID-19. Health care utilization is defined as any event such as hospitalization, ICU admission, ventilator use linked to any molecularly confirmed COVID-19 at least 14 days post-vaccination.

Assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo by first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) with onset at least 14 days after vaccination with study vaccine.

Assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection in participants with comorbidities associated with increased risk of progression to severe COVID-19, as compared to placebo defined as first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) in participants with comorbidities associated with increased risk of progression to severe COVID-19 with onset at least 14 days after vaccination with study vaccine.

To explore the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not previously described, as compared to placebo by first occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days after vaccination with study vaccine.

To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo by deaths occurring at least 14 days after vaccination with study vaccine.

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 by assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), 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 for 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, adenovirus neutralization as measured by VNA and 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 by 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 by presence, severity and duration of COVID-19 signs and symptoms and 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 by 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) for occurrence, severity, and duration of COVID-19 episodes, as assessed by a CEC.

5.5.1.2. Analysis Methods

For the assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed, mild COVID-19 by serial viral load measurements during the course of a COVID-19 episode the analysis method as described in section 5.4.4.4 will be repeated limited to the molecularly confirmed, mild COVID-19 cases.

For the first occurrence of any health care utilization linked to any molecularly confirmed COVID-19 defined as any event such as hospitalization, ICU admission, ventilator use linked to any molecularly confirmed COVID-19 at least 14 days post-vaccination, the proportion of participants

will be tabulated and an exact Poisson model will be performed. The ratio of incidence densities (IDR) will be computed for the vaccine versus placebo with the 95% exact CIs together with the percent reduction in health care utilization defined as 100*(1-IDR). If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) will be investigated. If enough cases per event type are available (more than 6) a separate model can be performed per event type.

For the assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo by first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) with onset at least 14 days after vaccination with study vaccine the analysis method as described in section 5.3 will be repeated using all SARS-CoV-2 infections. This analysis will be done using the PP and will be repeated in the FAS. These analyses will be repeated for participants with comorbidities associated with increased risk of progression to severe COVID-19 (as defined by the CDC, section 6.7).

For the assessment of the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not previously described, as compared to placebo by first occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days after vaccination with study vaccine the proportion of participants will be tabulated and an exact Poisson model will be performed. The ratio of incidence densities (IDR) will be computed for the vaccine versus placebo with the 95% exact CIs together with the percent reduction in respiratory disease defined as 100*(1-IDR). If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) will be investigated.

For the assessment of the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo by deaths occurring at least 14 days after vaccination with study vaccine, the proportion of participants will be tabulated and an exact Poisson model will be performed. The ratio of incidence densities (IDR) will be computed for the vaccine versus placebo with the 95% exact CIs together with the percent reduction in deaths defined as 100*(1-IDR). If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) and age group. All-cause deaths occurring at least 14 days after vaccination with study vaccine will be summarized by Kaplan-Meier method, and KM plot will be provided.

For the evaluation of 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 by assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), with the risk of COVID-19 and protection induced by the study vaccine participants with a COVID-19 episode immunogenicity data will be tabulated by vaccine regimen at baseline, 28 days post vaccination, on COVID-19 Day 3-5 and on COVID-19 Day 29 for the standard immunogenicity assays (S-ELISA and VNA) and on COVID-19 Day 3-5 and on COVID-19 Day 29 for all other assays that are available (Table 6). Immunogenicity data will be graphically displayed by vaccine regimen where actual values are shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay. 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. These analyses will be described in a separate correlates SAP for this purpose.

For the assessment of the humoral immune response to Ad26.COV2.S, as compared to placebo for 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, adenovirus neutralization as measured by VNA and analysis of antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein refer to section 5.7.1.

To assess the changes in the SARS-CoV-2 genome by development of SARS-CoV-2 variants a list of differentially expressed genes will be analyzed using parametric approaches to increase the power of detection. However, the false positive rate may be dramatically increased if the assumptions of the model distribution are violated. Based on the underlying distribution a method will be chosen and analysis details will be described in the DPS.

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 by presence, severity and duration of COVID-19 signs and symptoms and confirmation of SARS-CoV-2 infection by molecular testing refer to section 5.7.3.

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) for occurrence, severity, and duration of COVID-19 episodes, as assessed by a CEC. For severity we will look at the VE against at least severe, at least moderate, at least mild, at least symptomatic, and at least asymptomatic using the methods described in Appendix 8. The duration of COVID-19 episodes in days per regimen will be analyzed descriptively overall and per severity score with 95%CIs. Cases that were assigned a different evaluation by the CEC evaluation will be listed.

5.6. (Other) Safety Analyses

Following information will be collected for:

Participants in the Safety Subset:

- Solicited local and systemic adverse events (AEs) for 7 days after vaccination
- Unsolicited AEs for 28 days after vaccination

All participants in the FAS during the entire study:

- Serious adverse events (SAEs) and MAAEs leading to study discontinuation after vaccination

All participants in the FAS during the first 6 months:

– Medically-attended adverse events (MAAEs) after vaccination

Safety analyses will be performed on the FAS. No formal statistical testing of safety data is planned. Safety data by vaccination group will be analyzed descriptively. Specific safety analyses will be performed on the Safety Subset. All safety analyses will be tabulated by treatment group (active vaccine, placebo) according to the as-treated principle. All safety analyses will be presented overall and by age and comorbidity (with/without) strata. The main age strata for reporting purposes are ≥18 to <60 years of age and ≥60 years of age. In addition, safety data will be analyzed by treatment group and participant seropositivity status at screening.

Denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), 95% CI for the mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

Other exploratory or sensitivity analyses may be performed in addition to the analyses described below on an ad-hoc basis.

5.6.1. Adverse Events

5.6.1.1. Definitions

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at the injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their diary. Unsolicited AEs are all AEs for which the participant is not specifically questioned.

Solicited AEs shown in the tables are extracted from the investigator assessment pages (CE) of the CRF. For unsolicited AEs, only the AEs within the 28-day period following the vaccination will be presented in the safety tables except for SAEs and MAAEs leading to study discontinuation, which will be captured and tabulated in the outputs covering the whole study period and for all subjects in the FAS and MAAEs (including new onset of chronic diseases) which will be captured and tabulated in the outputs covering the 6 month post vaccination period and for all subjects in the FAS.

Solicited administration site symptoms will be by definition considered as related to the study vaccine.

The severity of the AEs will be classified as grade 1 to 4. Solicited events that are graded less than grade 1, are not considered as AE. In case no grades are available, the grading of the solicited events will occur according to the grading list in Appendix 6.

5.6.1.2. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated with exact 95% CI. Unsolicited AEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (administration site, systemic) and preferred term.

For solicited AEs following tables will be provided: summary, by worst severity grade, at least grade 3, related (systemic only), time to onset (in days) and duration (in days) for most frequent events (>5%) and body temperature. Note: Duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the vaccination period.

For unsolicited AEs following tables will be provided: summary table (including SAE, MAAEs, MAAEs leading to study discontinuation, fatal outcome, and discontinuation), all events, most frequent (>5%), at least grade 3, related and SAE. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

Listings and/or participant narratives will be provided as appropriate, for those participants who die, discontinue study due to an AE, or experience a serious AE.

5.6.1.3. Phase Allocation of Adverse Events

Solicited events are always allocated to the respective Post Dose period.

Step 1: Allocation of events to the periods:

Adverse events in the SDTM data base are allocated to periods based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

- In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.

- In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the trial. In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose 1 period), except if the end date of the AE falls before the start of the first active treatment phase (post dose 1 period).

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same participant with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day

after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

If overlapping/consecutive events start in one of the following periods - Screening or post dose extension (i.e. non-active periods) - followed by an AE in - post-dose period (active period) - they are allocated to their respective periods and are considered as separate events.

In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM data base but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

In case overlapping/consecutive events start in both an active period followed by a non-active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM data base but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.

In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.

Time is not considered when determining overlap of events.

5.6.1.4. Missing Data

Missing data will not be imputed. Participants who do not report an event/concomitant medication will be considered as participants without an event/concomitant medication. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade, but will be considered as not reported for the analysis of at least grade 3.

5.6.2. Vital Signs

No ECG are measured in this study. For HIV Viral Load and CD4 counts only abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the following gradings (absolute CD4+ Count: 300 – 400/mm3 (grade 1); 200 – 299/mm3 (grade 2) 100 – 199/mm3 (grade 3) and < 100/mm3 (grade 4) and for viral load when a subject goes from undetectable to detectable HIV RNA copies/mL.

For all participants, weight and height (and BMI) at baseline will be summarized using descriptive statistics. Vital sign abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the FDA grading table in Appendix 6.

Temperature will be measured at each scheduled time point and summarized using descriptive statistics. A listing of participants with fever will be provided. Other vital signs may be measured at the discretion of the investigator. For those, vital signs abnormalities of at least grade 3 will be listed.

For COVID-19 cases, temperature will be summarized over time from start of symptoms, using descriptive statistics and/or graphically. For temperature, 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 time point. Descriptive statistics will be calculated for changes between COVID-19 Day 29 and COVID-19 Day 3-5.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emerging. In case a laboratory test result is censored (no numeric value is available, but only a verbatim term) then a numeric value will be imputed by a value exceeding the cut-off value with one unit. (<x: subtract 1 unit from x, >x: add 1 unit to x; <3.45 is imputed with 3.44).

In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades, the following rules are applied:

Worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.

The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a participant has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.

If a lab value falls within the grading as specified in the grading table but also within the local lab normal limits, the value is considered as normal.

For the grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: in case limits under fasting and non-fasting conditions differ, the limits of the conditions (fasting/non-fasting) of scheduled visits as planned in the CTP will always be used, also for samples obtained under a different condition (e.g. samples of withdrawal visits).

5.7. Other Analyses

5.7.1. Immunogenicity

Blood will be collected from all non-Immuno Subset participants for humoral immunogenicity assessments before vaccination, 28 days after vaccination and at D71, W24 and W52 after vaccination. For a total of approximately 400 participants in the Immuno Subset, blood will be collected for analysis of humoral immune responses before vaccination, 28 days after vaccination, 70 days after vaccination, and 24, 52, 78, and 104 weeks after vaccination.

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 5.

Table 5: Overview of the Immunogenicity Assessments

Humoral Assays	**Purpose**
Secondary Endpoints	
SARS-CoV-2 binding antibodies to S protein (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing 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
Exploratory Endpoints	
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
Antibodies to the RBD of the SARS-CoV-2 S protein (ELISA)	Analysis of antibodies binding to the RBD of the SARS-CoV-2 S protein
Transcriptomic Assay	**Purpose**
Exploratory endpoints	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in unstimulated cells or whole blood

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

The analysis of immunogenicity will use the PPI set.

For the non-immuno subset, humoral immunogenicity data will be analyzed according to the as-treated principle by vaccine regimen (active vaccine, placebo), by vaccine regimen and participant seropositivity status at screening and by vaccine regimen and COVID-19 (no infection, asymptomatic infection, mild, at least mild, at least moderate, at least severe) and by vaccine regimen and age and comorbidity (with/without) strata, by vaccine regimen and region, by vaccine regimen and emerging CD4 count abnormality (at least grade 1 at any time after vaccination) and viral load

(treatment emergent detectable viral load). Specific immunogenicity analyses will be performed on the Immuno Subset. All immunogenicity analyses for the immuno subset will be analyzed by vaccine regimen and by vaccine regimen and age and comorbidity (with/without) strata.

For participants with a COVID-19 episode immunogenicity data will be analyzed by vaccine regimen at baseline, 28 days post vaccination, on COVID-19 Day 3-5 and on COVID-19 Day 29 for the standard immunogenicity assays (S-ELISA and VNA) and on COVID-19 Day 3-5 and on COVID-19 Day 29 for all other assays that are available (Table 6).

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. These analyses will be described in a separate correlates SAP.

5.7.1.1. Parameters

The following humoral immune responses are measured by immunogenicity against the insert using humoral immune responses, including titers of neutralizing antibodies and S-ELISA titers, functional and molecular antibody characterization and RBD antibodies and N-ELISA positivity. Immunogenicity against the vector will be explored using an adenovirus neutralization assay to assess neutralizing antibody responses against the vector.

5.7.1.2. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Values will be imputed based on the type of analysis. For the calculation of the geometric mean titer, values below LLOQ will be imputed to LLOQ/2. While for the calculation of the geometric mean of the increase from baseline, values below LLOQ will be imputed to LLOQ. The LLOQ values per assay are available in the data base.

Data above the ULOQ will be imputed with the ULOQ.

5.7.1.3. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

5.7.1.4. Immunogenicity Against the Insert:

5.7.1.4.1. Humoral assays

For **VNA (**both wild-type virus and pseudovirion expressing S protein, as available) and **S-ELISA** assays following results will be calculated: N, geometric mean[a§]and corresponding 95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented.

[a] calculate the mean and corresponding 95% CI of the $\log^{10}$ transformed values, back-transform this mean [i.e. 10^mean] and CI [i.e. 10^CI].

For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the log10 transformed values. These values are back transformed to provide the geometric mean and its corresponding 95% CI.

For wild type, pseudovirion VNA and S-ELISA separately:

• A sample will be considered positive if the value is strictly greater than the LLOQ (>LLOQ).

• Responder definition. A post-baseline sample will be considered a responder if at least one of the following conditions is satisfied:

- The baseline sample value is less than or equal to the LLOQ (≤LLOQ) and the post-baseline sample is strictly greater than the LLOQ (>LLOQ)

- The baseline sample value is strictly greater than the LLOQ (>LLOQ) and the post-baseline sample value represents an at least 4-fold (≥4-fold) increase from the baseline sample value.

Actual values are tabulated and shown as box plots with the corresponding geometric mean, 95% CI per time point and minimum and maximum are shown for each assay. For the immuno subset actual values are tabulated and shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay.

In addition, GMT plots over time, combining the regimens in one graph (without individual participant dots) will also be generated.

Participant profiles of the actual values over time will be graphically presented for Covid-19 cases.

Correlation plots between humoral assay results will be provided for selected time points.

In the graphs, original values will be displayed on the log10 scale.

Further details may be provided in the DPS. In the graphs, original values will be displayed on the $\log^{10}$ scale.

For the **N-ELISA** the proportion of participants that are positive will be tabulated.

5.7.1.5. Immunogenicity Against the Vector

For immunogenicity against the Ad26 vector backbone (Adenovirus neutralization by neutralization assay) following statistics will be calculated: geometric mean and corresponding 95% CI of the actual values, and number and percentage of participants with a positive sample.

Correlation plots with the Adeno assays versus the assays against the inserts will be provided for the most important time points.

5.7.2. Definition of Subgroups

Selected safety and efficacy analyses will be summarized by treatment group for the following subgroups:

- sex
- race
- ethnicity
- age categories 1 (18-≤59, ≥60years)
- age categories 2 (18-<40, 40-≤59, ≥60 years)
- age categories 3 (18-<40, 40-≤59, 60-≤69, 70-≤79, ≥80 years)
- region (Africa, North-America, Latin-America, Europe (if applicable), Asia (if applicable)). Regions may be modified/pooled based on participation.
- presence of baseline comorbidity
- seropositivity status (positive vs. negative)

If necessary for country approval/submission, an analysis by country may be added.

5.7.3. Patient-Reported Outcomes

5.7.3.1. Symptoms of Infection with Coronavirus-19 (SIC)

The SIC consists of 3 separate parts (symptoms rated from 0 to 10 as part 1, fever as part 2, and 4 separate symptoms as part 3) that are scored separately:

- Part 1: Each symptom is present or absent (0), and if present rated on a 10 point scale from ranging from 0 (None) to 10 (Worst possible).

The **symptom score** is the mean of all scores for each day, during the COVID-19 episode.

The **symptom duration** is the period from the first day of symptoms till the last day with symptoms in Days (calculated as last day with symptoms – first day of symptoms + 1).

The **symptom AUC** is the area under the curve for the complete COVID-19 episode.

The **peak symptom score** is the maximum of all the symptom scores during the COVID-19 episode.

- Part 2: Fever.

Fever will be scored (fever score) as the maximum recorded temperature for each day during the COVID-19 episode.

Fever will be coded as 'Present' if the fever score is ≥38.0 ^{o}C or ≥100.4 ^{o}F and 'Absent' otherwise.

The **total fever days** is the number of days with fever present during the COVID-19 episode.

Fever duration will be the period from the first day with fever till the last day with fever in Days (calculated as last day with fever – first day of fever + 1).

The **peak fever** is the maximum fever score during the COVID-19 episode.

The **fever AUC is** the AUC of fever score during the total of fever days of the COVID-19 episode. (For the AUC if there is a single missing day between days with fever the missing day will be ignored, i.e., interpolation will be used in the calculation of the AUC.)

The fever score will also be coded using FDA grades for fever.

- Part 3: Each of the 4 specific symptoms is rated on the following scale, 0=None, 1=Mild, 2=Moderate, 3=Severe. (The answer 'No' to the presence of a specific symptom is coded as 0 or None.)

The **specific symptom score** is the mean of all scores during the COVID-19 episode per day.

The **total specific symptom score** is the mean of all scores during the COVID-19 episode.

The **total specific symptom duration** is the duration of specific symptoms during the COVID-19 episode from the first day with a specific symptom till the last day with a specific symptom in Days (calculated as last day with a specific symptom – first day of a specific symptom + 1).

The **total specific reported symptom score** is the mean of all scores during the COVID-19 episode at which a subject has reported at least one specific symptom.

Note 1: For Part 1, total scores will be calculated based on the number of assessments completed by the participant per day and in cases where more than 75% of the items needed to calculate the score is not collected (reported as no answer to the part 1 Yes/No possibility AND no severity rate), then the value for that score will be set to missing. For example, if a participant has responded to 7 or more out of the 25 symptom scale questions the score will be the mean of the available questions. If the participant has only completed 6 or less of the questions then the symptom score will be set to missing, unless a subject has only provided responses 'Yes' to all of the answered questions (then it is assumed that the subject only noted the pertinent symptoms for that day). In case of missing severity rate and the answer was 'yes' the rate will be imputed by '5'.

5.7.3.2. Analysis Methods

SIC scores will be analyzed for participants with any COVID-19 episode based on the PP set.

For continuous variables, number of observations, mean, standard deviation, median, first and third interquartile will be tabulated and means with standard errors will be graphically presented per vaccine regimen and means with standard errors will be graphically presented per group and time point (starts since onset of COVID-19 episode). Counts will be tabulated.

These analyses will also be summarized by COVID-19 for each classification (mild, moderate, severe-critical cases) and additionally in a cumulative fashion (at least mild, at least moderate, and all symptomatic cases).

In case a participant experiences two or more episodes, all episodes will be analyzed according to the definitions above. For summaries across treatment groups, the episode classified with the highest severity will be selected. If the worst severity is equal for several episodes, scores of these episodes will be averaged for the participant before calculating overall averages.

5.8. Interim Analyses

Interim analyses are performed in the form of continuous monitoring and are provided in Table 6. No other interim analyses are planned.

Table 6: 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 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 receive the vaccine.	one-sided p-value compared to α at 5%, no multiplicity adjustment	After every event starting from the 5th event
Non-efficacy	FAS in seronegatives only	H_0: VE ≥40% vs. H_1: VE <40%	Exact 95% CI	Upper limit of the 95%CI <40%	Every week, starting from the 20th event after 14 days post dose 1[b]
Efficacy[d]	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 14 days post dose 1 are observed, **then at least weekly thereafter**[d]

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.
[b] Monitoring stops when the primary efficacy analysis is triggered.
[d] The efficacy monitoring can only start if at least 2 months of follow-up after vaccination of the first 50% of planned participants has been observed, a minimum of 6 moderate to severe/critical cases (combined randomized groups) for the ≥60 years age group occurred, and 5 severe/critical cases occurred.

All boundaries will be monitored by the Statistical Support Group (SSG). If a boundary has been crossed, then the SSG immediately informs the Chair of the DSMB through secure communication procedures. At this point the DSMB will convene, evaluate the totality of the data and provide a recommendation to the Sponsor.

The study team is responsible for providing the blinded information to the SSG. For relevant definitions regarding a case assignment, see Section 5.1.3.

5.8.1. Assigning cases for continuous monitoring

Definitions and general case assignment rules are described in Section 5.1.3.

For continuous monitoring the order of cases will be based on the *onset of symptoms*. An episode of COVID-19 may however start with mild symptoms and may deteriorate to a degree that it

satisfies a more severe classification. To avoid situations that an event occurs that already should have been analyzed as based on the onset of symptoms, the approach chosen here is that each case will be analysis-ready at **Day 15** (see also CTP Section 8.1).

For this approach it is of concern if an event is not resolved at Day 15, AND if that event worsens in severity after Day 15. In the rare case that this happens AND affects one of the 4 monitoring processes, the case will be added based on the moment it is established that it satisfies a more severe definition.

Continuous monitoring will be performed on analysis-ready cases known up to that and including that calendar Day; if multiple cases are analysis-ready on a Day, the boundary will be verified for the total number of cases.

For the monitoring of potential severe harm, the event will be entered in the monitoring as soon as the events becomes confirmed as satisfying the severe/critical case definition.

The period of 14 Days for an episode of COVID-19 to take its course is chosen as it is expected to have limited impact on case classification, and it also allows to assess critical information that is required to determine if the case is part of a continuous monitoring process (and how it should be entered):

- Was the participant included in the FAS? (Note that this means that the participant was randomized and treated.)
- Was the participant treated with the assigned treatment? (Note that if not, the participant would be analyzed *as treated* in the FAS and excluded from the PP population.)
- Was the volume of the injection sufficient (≥80%) according to the drug administration log?
- Was the participant seronegative at baseline?
- Was the participant part of the PP population (see Section 4)?
- Was the onset of symptoms post-vaccination (Day 2 or later)?
- Was the onset of symptoms after Day 14 (Day 15 or later)?

5.8.2. Harm monitoring for excess symptomatic COVID-19 cases

Continuous monitoring for vaccine-associated *enhanced* COVID-19 will be performed based on *symptomatic* COVID-19 events in the FAS population. Only cases where the onset of symptoms is on Day 2 or later will be included. Monitoring for harm will be performed on a daily basis on analysis-ready cases only.

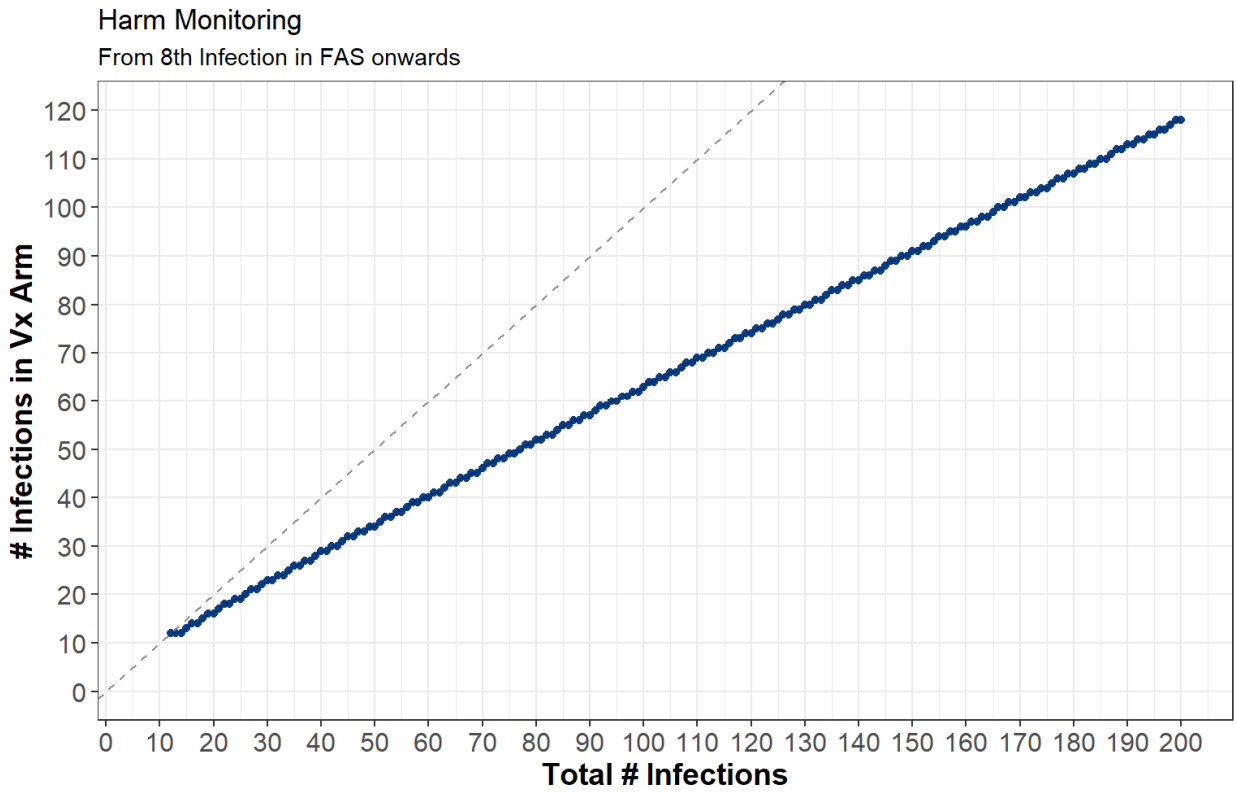
The monitoring starts when there are in total 12 analysis-ready symptomatic cases observed and will continue to be monitored on each calendar day until the primary analysis is triggered. In order to calculate the boundaries for this monitoring while controlling overall alpha level as specified

(i.e. 5% overall alpha) an assumption must be made on maximum number of looks that will have to be made. For this purpose, it is assumed that there will be a maximum of 200 symptomatic cases before the primary analysis is triggered. This leads to the following boundaries on the number of events in the active treatment group for each total number of events. Starting at 12 analysis-ready cases, the boundary is crossed if there are 0 or 1 analysis-ready cases on placebo and all other cases are on active treatment. If there are 2 analysis-ready cases on placebo, the boundary is crossed if the total is 14 cases (i.e., 12 on active), etcetera (Table). The boundary is illustrated graphically in Figure 4.

Table 6: The number of Symptomatic Cases on Placebo and Total number of Symptomatic Cases at which Point the Boundary is Crossed (FAS)

Placebo	Total	Placebo	Total	Placebo	Total	Placebo	Total
≤1	13	22	65	43	113	64	160
2	14	23	67	44	115	65	162
3	17	24	69	45	118	66	164
4	20	25	72	46	120	67	167
5	23	26	74	47	122	68	169
6	25	27	76	48	124	69	171
7	28	28	79	49	127	70	173
8	31	29	81	50	129	71	175
9	33	30	83	51	131	72	178
10	36	31	86	52	133	73	180
11	38	32	88	53	136	74	182
12	41	33	90	54	138	75	184
13	43	34	93	55	140	76	186
14	46	35	95	56	142	77	189
15	48	36	97	57	144	78	191
16	50	37	99	58	147	79	193
17	53	38	102	59	149	80	195
18	55	39	104	60	151	81	197
19	58	40	106	61	153	82	200
20	60	41	109	62	156		
21	62	42	111	63	158		

Figure 4: Harm Monitoring Boundary - Active versus Total Number of Symptomatic Cases (FAS)



5.8.3. Harm monitoring for excess severe COVID-19 cases

Vaccine harm monitoring is intended to monitor for vaccine-induced enhanced disease and will be performed for severe/critical COVID-19 cases based on the FAS each calendar day. Specifically, monitoring for a higher rate of severe/critical disease or death starts at the 5th event, until the harm boundary is reached, or until the primary efficacy analysis is triggered. Monitoring for harm of severe/critical COVID-19 cases will be performed on a daily basis on all available severe cases, irrespective of their analysis ready status.

The monitoring excess severe is done using an exact one-sided binomial test of the null hypothesis $H_0: p \leq 1/2$ versus the alternative hypothesis $H_1: p > 1/2$, where p is the probability that an -infected participant was assigned to the vaccine arm (as opposed to being assigned to the placebo arm). The testing for harm starts at the 5th total severe cases in the FAS and is performed continuously through the primary analysis. Each test is performed at an uncorrected one-sided significance level of $\alpha = 0.05$.

5.8.4. Non-efficacy monitoring

The non-efficacy monitoring is based on analysis-ready moderate/severe cases in the FAS, where a participant must be seronegative at baseline to be included in this boundary monitoring. Every effort will be made to establish seronegativity in time. In the unlikely case seronegativity is not established in time for a case that is to be included in a monitoring calculation otherwise (ie, on

Day 14 of an episode), the case will only be included for non-efficacy monitoring at the time seronegativity is established; monitoring calculations will not be repeated at that time.

This boundary will be verified starting once 20 analysis-ready moderate/severe cases in the FAS (seropositive) are observed. From that point onwards, after at least weekly, the boundary will be checked on analysis-ready cases. Monitoring for non-efficacy stops when the primary analysis is triggered. The boundary for non-efficacy is provided in Table 7 and illustrated in Figure , and is based on the case splits that trigger the rules as defined in Table 6 using the methods laid out in Appendix 8 with the exact binomial based confidence intervals.

Table 7: The Number of Confirmed Moderate/Severe Cases on Placebo and Total Number of Confirmed Moderate/Severe Cases at which Point the Non-efficacy Boundary has been Crossed (FAS – seronegative)

Placebo	Total	Placebo	Total	Placebo	Total	Placebo	Total
≤7	20	27	56	47	91	67	126
8	21	28	58	48	93	68	127
9	23	29	60	49	95	69	129
10	25	30	61	50	96	70	131
11	27	31	63	51	98	71	132
12	29	32	65	52	100	72	134
13	31	33	67	53	102	73	136
14	32	34	68	54	103	74	138
15	34	35	70	55	105	75	139
16	36	36	72	56	107	76	141
17	38	37	74	57	108	77	143
18	40	38	75	58	110	78	144
19	42	39	77	59	112	79	146
20	43	40	79	60	114	80	148
21	45	41	81	61	115	81	150
22	47	42	82	62	117	82	151
23	49	43	84	63	119	83	153
24	51	44	86	64	120	84	155
25	52	45	88	65	122	85	156
26	54	46	89	66	124	86	158

Figure 5: Boundary for Non-Efficacy (FAS, seronegative)

5.8.5. Efficacy monitoring

As the efficacy monitoring is linked to the primary endpoint, the statistical details on efficacy monitoring are already described in the corresponding section, section 5.3.

Table 8 describes the number of analysis-ready primary endpoints required as a fraction of the total number of cases in order to stop and reject the primary study hypothesis.

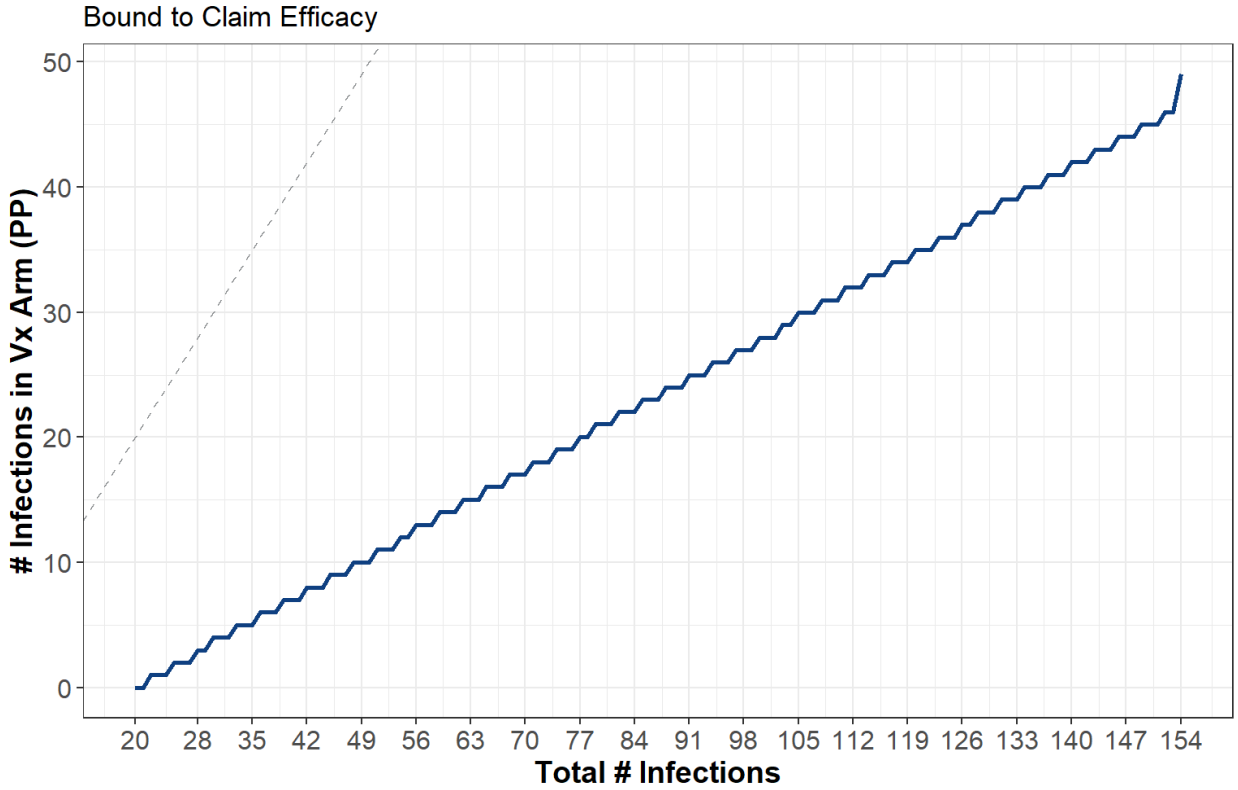
If the prespecified boundary is met in the situation that the constraints have also been met (a minimum of 6 molecularly confirmed, moderate to severe/critical COVID-19 cases in the population of participants aged 60 years or older, a minimum of 5 of molecularly confirmed severe/critical COVID-19 cases in the placebo group with a favorable split, and a median follow-up time of 2 months after vaccination of the planned sample size), the SSG will inform the DSMB and, if deemed appropriate by the DSMB, a meeting with the DSMB 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. The study team will remain blinded until the database for primary analysis is locked.

Table 8: The Number of Confirmed Moderate/severe Cases on Active and Total Number of Confirmed Moderate/severe Cases at which Point the Efficacy Boundary has been Crossed (PP)

Active	Total	Active	Total	Active	Total
0	20	16	65	32	111
1	22	17	68	33	114
2	25	18	71	34	117
3	28	19	74	35	120
4	30	20	77	36	123
5	33	21	79	37	126
6	36	22	82	38	128
7	39	23	85	39	131
8	42	24	88	40	134
9	45	25	91	41	137
10	48	26	94	42	140
11	51	27	97	43	143
12	54	28	100	44	146
13	56	29	103	45	149
14	59	30	105	46	152
15	62	31	108	49	154

The blinded total number of infections in the FAS with onset of infection after study vaccination may be monitored to track progress and ensure timely cleaning to facilitate operationalization of data base lock.

Figure 6: Boundary for Efficacy (PP)



5.8.6. Sample size monitoring

Given the maximum sample size selected it is considered unlikely that the blinded sample size re-estimation will occur.

5.8.7. Data and Safety Monitoring Board (DSMB)

The study will be formally monitored by a DSMB (also known as an Independent Data Monitoring Committee or IDMC). In general, the DSMB will monitor safety data on a regular basis to ensure the continuing safety of the participants. Enrollment (if applicable) will not be paused during regular safety reviews. The DSMB will review unblinded data. The DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter and DSMB Charter Addendum.

The DSMB will also review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b is initiated, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

Continuous monitoring of safety and (non-) efficacy is described in detail in Section 5. If a boundary is met, the SSG immediately informs the DSMB through secure communication procedures. At this point a quorum of the DSMB will be convened as soon as possible and provide a recommendation to the Oversight Group. See also Section 9.8 of the CTP.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ATC	anatomic and therapeutic class
BMI	body mass index
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CI	confidence interval
CRF	case report form
CTP	clinical trial protocol
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
GMC	geometric mean antibody concentration
GMT	Geometric Mean Titer
FAS	full analysis set
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
HR	hazard ratio
ICF	informed consent form
IDMC	Independent Data Monitoring Committee (and similar to DSMB)
IFNg	interferon gamma
IL2	interleukin 2
IRR	incidence rate ratio
ITT	intent-to-treat
LLOQ	lower limit of quantification
NA	not applicable
PBMC	peripheral blood mononuclear cells
PP	per protocol efficacy analysis set
PPI	per protocol immunogenicity analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SFU	spot forming units
SN	seronegative
SP	seropositive
TNFa	tumor necrosis factor alpha
ULOQ	upper limit of quantification
VE	vaccine efficacy
VNA	virus neutralizing antibody
vp	virus particle
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

SAP according to EDMS-RIM-50860, Amendment 1

6.3. Appendix 3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Table 9 presents a list of the demographic variables that will be summarized by vaccine regimen and overall for the FAS. Demographics will also be summarized by region using the FAS.

Table 9: Demographic Variables

Continuous Variables:	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age ([18-25 years, 26-50 years, 51-64 years, and ≥=65 years])	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, unknown, intersex)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2])	
Working Status	
Profession	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.4. Appendix 4 Protocol Deviations

Major protocol deviations and major protocol deviations potentially impacting immunogenicity or efficacy (see section 4) will be summarized.

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to data base lock and the participants with major protocol deviations will be summarized by category.

[Developed withdrawal criteria but not withdrawn]

[Entered but did not satisfy criteria]

[Received a disallowed concomitant treatment]

[Received wrong treatment or incorrect dose]

[Other]

6.5. Appendix 5 Prior and Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

For all participants, concomitant therapies associated with an SAE will be collected and recorded in the eCRF from the moment of vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study. The proportion of participants with concomitant medication associated with these SAEs and MAAEs will be tabulated with exact 95% CI.

For all participants, concomitant therapies associated with COVID-19 will be captured in the electronic eCRF for the duration of the study. The proportion of participants with new concomitant medication associated with these cases will be tabulated with exact 95% CI. New concomitant medications are defined as medications not available at baseline or medication with an increased dosage (See below, New Concomitant Medications, for details), compared to baseline. Baseline medications are all medications reported prior to and at the day of vaccination. In case a baseline medication is reported multiple times then only the last available record reported prior to or at the day of vaccination will be used.

For participants in the Safety Subset, concomitant therapies associated with unsolicited AEs will be collected, recorded in the eCRF from the time of vaccination through 28 days after vaccination and the proportion of participants with concomitant medication will be tabulated with exact 95% CI. Concomitant therapies associated with solicited AEs will be collected by the participants, recorded in the eCRF from the time of vaccination through 7 days after vaccination and the proportion of participants with concomitant medication will be tabulated with exact 95% CI.

Based on their start and stop date, concomitant therapies will be reported in each applicable phase.

If a concomitant therapy record misses components of its start and/or stop dates (time, day and/or month and/or year):

In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods. In case it is clear the medication was taken after vaccination, the start will be allocated to the correct phase without the use of the start dates (time, day and/or month and/or year). In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

There will be special attention to any systemic use of analgesics/antipyretics, started during 8 days following each vaccination (00:00 of day of vaccination + 7 days). Following CMCLASCD (ATC/DD codes) will be used for this: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC

PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION). The classes will be added in a footnote in all related tables and listings. For the use of analgesics/antipyretics which are taken on the day of vaccination an exception is made in case the time is before vaccination. In this case the concomitant medication is also allocated to the post-dose period.

New Concomitant Medications – Increase in dosage Calculation

In case a participant receives the same medication with the same form at baseline and during an COVID-19 episode, then in order to identify whether there was an increase in dose between baseline and the episode the medication dose will be calculated by multiplying the dosage per administration with the number of administrations per day or per week, as applicable for both timepoints and compared.

This rule applies for the following medication frequencies:

- Once weekly (1 time per week)
- Twice weekly (2 times per week)
- Three Times weekly (3 times per week)
- Four Times weekly (4 times per week)
- Twice Daily (BID)
- Twice per Month (BIM)
- Every two weeks (Every 2 weeks)
- Every four weeks (Every 4 weeks)
- Weekly (Every week)
- Once
- Per Year
- Every three months (Q3M)
- Daily (QD)
- Four times daily (Q1D)
- Monthly (QM)
- Every Other Day (QOD)
- Three times daily (TID)

For frequencies equal to ‘other’at baseline, any change to one of the above frequencies will beconsidered an increase, given that the form remains the same. For frequencies equal to ‘as necessary’ (PNR) or ‘occasional’, any change to another frequency or dose will be considered as an increase. A change from ‘as necessary’ (PNR) to ‘occasional’ or ‘other’ will not be considered as an increase.

Moreover, capsule and tablet are considered the same form so to define if there was an increase the dose and the frequency will be used as defined above. The same applies for inhalant and aerosol.

6.6. Appendix 6 FDA Toxicity Grading Scale for Vaccine Trials

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.

6.7. Appendix 7 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. * Smoking and controlled grade 1 hypertension are allowed per protocol and are not exclusion criteria.

6.8. Appendix 8 Statistical Methodology for Poisson Regression

Vaccine efficacy is defined as 1 minus the ratio of the expected incidence rate of cases of COVID-19 in the active group compared to the expected incidence rate in the placebo group.

Vaccine efficacy can be estimated by:

$$\widehat{VE} = 1 - \frac{n_2/N_2}{n_1/N_1} = 1 - \frac{r * n_1}{n_2}$$

Where:

n_2 = number of cases in the vaccinated group
N_2 = follow-up time in the vaccinated group
n_1 = number of cases in the control group
N_1 = follow-up time in the control group
r = $\frac{N_1}{N_2}$.

Let $n = n_1 + n_2$ denote the total number of cases. Suppose that $n_i|N_1, N_2 \sim Poisson(N_i p_i)$, $i = 1,2$, so that $VE = 1 - p_2/p_1$. In this case, conditionally on n and r, n_2 is binomially distributed as $B(n, \pi)$, where $\pi = N_2 p_2/(N_1 p_1 + N_2 p_2) = (1 - VE)/(r + 1 - VE)$.

Let $q = n_2/n$ denote the proportion of cases in the vaccine group. Then, the vaccine efficacy estimator can be rewritten as:

$$\widehat{VE} = 1 - \frac{n_2}{n} * \frac{r * n}{(n - n_2)} = 1 - \frac{r * q}{(1 - q)}$$

Therefore, there is a monotonically decreasing link between the estimated VE and $q = n_2/n$, the observed proportion of cases in the vaccine group among the total cases, and so rejecting a hypothesis for extreme values of q is equivalent to rejecting that same hypothesis for inversely extreme values of $\widehat{VE}$.

Given the sequential testing strategy, the confidence interval for the vaccine efficacy will be adjusted accounting for repeated testing. At the primary analysis when the boundary is crossed or at 104 events, the vaccine efficacy estimate will be reported using the estimated VE (as detailed above) at the time of analysis, accompanied with $(1 - \alpha^*)\%$ one sided CI, where alpha* is the type I error at that time. Using the exact binomial CI for p an (adjusted) exact Poisson regression CI can be constructed (Dragalin et al, 2002; Nauta, 2011).

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Janssen Research & Development

Statistical Analysis Plan

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

Protocol VAC31518COV3001; Phase 3

VAC31518 (JNJ-78436735)

Status:	Approved
Date:	15 January 2021
Prepared by:	Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study
Document No.:	EDMS-RIM-137421

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	23AUG2020	Not Applicable	Initial release
2	18SEP2020	Clinical Trial Protocol Amendment 1	Clinical Trial Protocol Amendment 1
3	30OCT2020	Changes to hypothesis testing strategy, adding a supportive analysis to the primary analysis based on cases that were not analysis ready at data base lock and clarifications / corrections	Including feedback received from Health Authorities
4	16 Dec 2020	Aligning analysis on any SARS-CoV-2 infection with protocol. Updates to SAP in line with protocol amendment 3, including a sample size reduction from 60,000 to approximately 40,000 participants and introduction of co-primary endpoints	Any SARS-CoV-2 infection: SAP and protocol were not aligned. Changes to protocol amendment 3.
5	14 Jan 2021	Clarifying that for not analysis-ready cases, central confirmation by the University of Washington is not needed Changed the identification of severe cases through programming and medical review. Adding CBER feedback: - Additional success criterion on the point estimate for the primary endpoint	Clarifications and feedback from FDA on severe case definition and SAP

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analysis methods for evaluation of the primary, secondary and exploratory objectives of the phase 3 study designed to assess in a randomized, double-blind, placebo-controlled manner the efficacy and safety of the Ad26.COV2.S candidate vaccine.

The vaccine has been designed for the prevention of SARS-CoV-2 mediated coronavirus disease 2019 (COVID-19) in adults aged 18 years and older. This SAP will detail the analytical plan for interim monitoring, the inferential study objectives as well as the statistical methods for the primary analysis based on all available data at the time of data base cut off (see Section 2). Sponsor personnel will be unblinded at the time of the primary analysis. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an analysis will be performed (referred to as "snapshot analysis") and sponsor personnel will be unblinded at the time of the snapshot analysis. Investigator and participants remain blinded until study completion (end-of-study analysis). The unblinding strategy of the sponsor will be described in a separate document.

This analysis plan also includes the technical details for the statistical analysis plan associated with the interim monitoring evaluation for harm, non-efficacy and efficacy to support the data and safety monitoring board (DSMB).

This randomized, placebo-controlled clinical trial is designed to enable expeditious safety, efficacy and immunogenicity evaluation of the Ad26.COV2.S candidate preventive vaccine against COVID-19 at sites with high COVID-19 attack rates, to ensure the observation of COVID-19 cases to assess the role of a vaccine in containing the pandemic. Boundaries are set up to monitor for excess harm, non-efficacy and efficacy. If a prespecified boundary is met for harm or non-efficacy or the prespecified boundaries are met for efficacy, the statistical support group (SSG) will inform the DSMB. The DSMB will provide a recommendation to the Oversight Group. The Oversight Group can trigger decision procedures to initiate health authority interactions based on the outcome of the study. The sponsor will remain blinded until the data base for the primary analysis is locked or until the time of the snapshot analysis.

The primary objective of the trial is to evaluate the vaccine's effect on the rate of virologically-confirmed moderate to severe/critical COVID-19, in adults at high risk for infection and/or disease.

The co-primary endpoints 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 vaccination (from Day 15) with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID 19 according to the case definition, with onset at least 28 days after vaccination (from Day 29)

with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

The trial will enroll and randomize large numbers of adult participants in different populations. Until 1 year post-vaccination or until the primary analysis takes place (whichever comes last), 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 post-vaccination or after the primary analysis takes place (whichever comes last), until the end of the long-term follow-up period, the frequency of this surveillance question through the eCOA will decrease to once every 2 weeks. Vaccine efficacy to prevent mild COVID-19, to prevent COVID-19 of any severity (burden of disease), to prevent acquisition of asymptomatic SARS-CoV-2 infection, to prevent COVID-19 requiring medical intervention, to prevent acquisition of any SARS-CoV-2 infection and to investigate SARS-CoV-2 viral load for moderate to severe/critical COVID-19 cases are secondary objectives. The design has continuous monitoring of events to report results upon early evidence of vaccine efficacy, lack of efficacy, or vaccine safety concerns. The trial is powered to provide sufficient evidence of safety and vaccine efficacy to prevent COVID-19 in support of possible (potential) marketing authorizations. Note that in Protocol Amendment 3, the sample size was reduced from 60,000 to approximately 40,000 participants.

The study will have the following timepoints for efficacy analyses:

1. The evaluation of the primary objective will be performed as soon as the target number of events (TNE) has been reached for both co-primary endpoints, or earlier based on sequential monitoring of both co-primary endpoints. Sponsor unblinding will occur but investigator and participants remain blinded until study completion. The unblinding strategy of the sponsor will be described in a separate document.

2. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached (8-week median follow-up timepoint). If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

3. After the primary analysis, additional analyses to support health authority interactions may be planned, if deemed appropriate.

4. The final analysis will be performed when the last participant completes the visit 12 months post-vaccination or discontinues earlier.

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

1.1. Objectives and Endpoints

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

To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe/critical COVID-19[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
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[b], at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], mild COVID-19[b], at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition[d]	• First occurrence of molecularly confirmed[a] COVID-19[b] at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a] COVID-19[b] at least 28 days post-vaccination (Day 29)
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[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 post-vaccination (Day 15). • 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 28 days post-vaccination (Day 29).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 28 days after vaccination (Day 29)
Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination,	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days

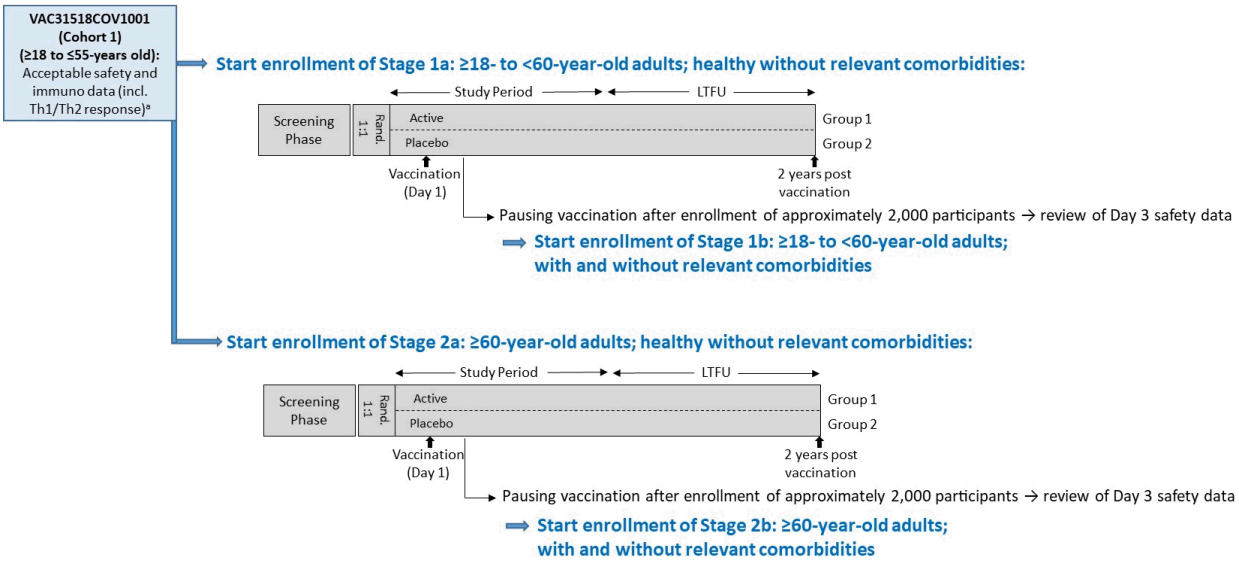
and in terms of unsolicited AEs during 28 days post-vaccination	following vaccination and of unsolicited AEs during 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	– Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result 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 in the CTP).
[c] Per case definition for mild COVID-19 (see Section 8.1.3.2 in the CTP).
[d] Per case definition for COVID-19 according to the US FDA harmonized case definition (see Section 8.1.3.3 in the CTP).
[e] All secondary endpoint analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated.
[f] For more information and the definition of the BOD endpoint, refer to the Section 9.5.2 Secondary Endpoints in the CTP.

1.2. Study Design

This is 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. An overview of the design is provided in Figure 1.

Figure 1 Schematic Overview of the Study



Participants will be vaccinated with one vaccination according to a 1:1 randomization:

- 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 Ad26.COV2.S or placebo at Day 1, using the same volume (ie, 0.5 mL).

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 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 15 (see CTP).

The randomization system will be used to control the age distribution of participants in the trial; in particular the age ranges of ≥18 to <40 and ≥40 to <60 years can be closed separately for further randomization in order to obtain a distribution of approximately 20% and 50% for these age ranges, respectively, and to have a minimum of approximately 30% of the population to be ≥60 years.

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.

2. STATISTICAL HYPOTHESES

The co-primary endpoints will evaluate

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition (Section 8.1.3.1 in the CTP), with onset at least 14 days post vaccination with Ad26.COV2.S or placebo, in the Per Protocol (per protocol (PP) population (see Section 4), including all events from both age groups, with and without comorbidities.

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition (Section 8.1.3.1 in the CTP), with onset at least 28 days post vaccination with Ad26.COV2.S or placebo, in the Per Protocol (per protocol (PP) population (see Section 4), including all events from both age groups, with and without comorbidities.

A successful primary efficacy conclusion will require:

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

AND

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

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

To evaluate the primary null hypotheses: H_0: VE ≤30% versus H_1: VE >30% for the co-primary endpoints, the truncated sequential probability ratio test will be used based on accumulating event data for each co-primary endpoint. 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=60% using a one-sided alpha=0.025 against H0:VE≤30%, with appropriate control of the type-1 error rate (alpha) for interim monitoring. The same boundary will be used for each co-primary endpoint.

For the evaluation of the favorable ratio against the severe/critical COVID-19 endpoints a sequential boundary corresponding to a VE point estimate ≥50% and a minimum of 5 events in the placebo group will be prespecified. This is further detailed in section 5.4.3.

If an efficacy signal is triggered before the required 8-week follow-up after vaccination for approximately 50% of enrolled participants is reached, an additional analysis will be performed when that follow-up timepoint is reached, to support health authority interactions. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis. The co-primary endpoints will then be re-evaluated against the null hypothesis: H_0: VE ≤30% versus H_1: VE >30% using the sequential probability ratio test with the total number of events at that time.

If the co-primary endpoint hypothesis testing reaches significance for both co-primary endpoints, with the respective data requirements met, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%.

For each secondary endpoint in the confirmative endpoint section 5.5.2, the hypothesis of vaccine efficacy (VE) H_0: VE ≤0% versus H_1: VE >0% will be evaluated in the PP set, including all events as defined in the vaccine evaluation window for the respective endpoint at the time of the primary analysis.

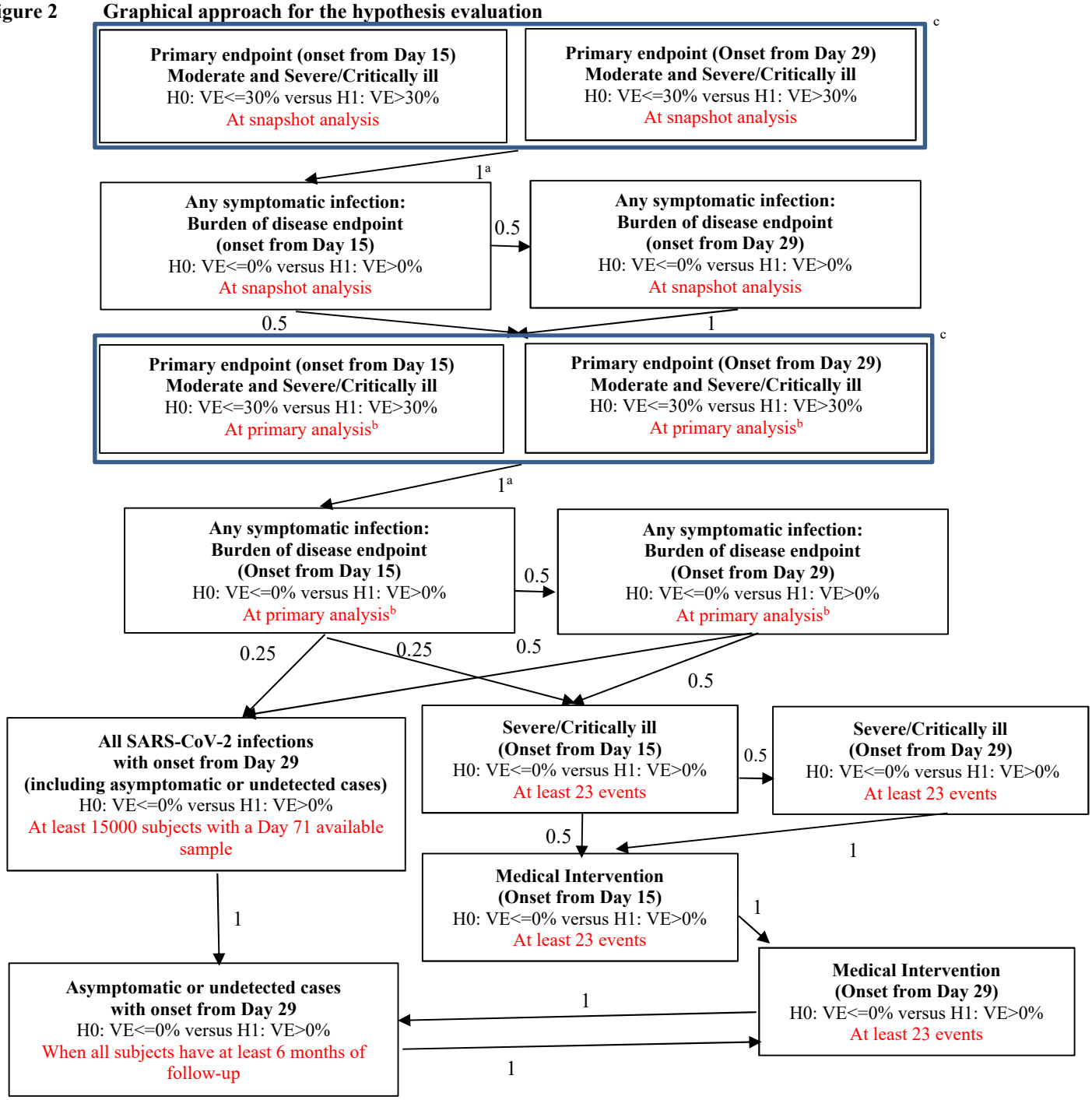
The evaluation of secondary endpoints will be adjusted for multiple testing of multiple endpoints (using a graphical approach, Bretz et al 2009) and potential stopping at an interim analysis evaluation through a Pocock boundary using Wang-Tsiatis with Delta=0.5.

The timepoint and order of evaluation of multiple endpoints will be done according to the graphical method that is detailed below in Figure 2.

The alpha level that will be passed down to the secondary tests is based on a GSD with a single interim analysis and with information fraction determined by the primary endpoint including all events with onset at least 28 days post vaccination (i.e., number of available primary events with onset at least 28 days post vaccination at the time of data base cut off (when the respective efficacy boundary is crossed by each co-primary endpoint and the data requirements are met) divided by the TNE of 154) and corresponding alpha-level obtained from Wang-Tsiatis bounds with delta=0.5. If more than 154 primary endpoints with onset at least 28 days post vaccination are observed at the time of data base cut off (e.g. when the minimal data requirements for either co-primary endpoint are not met prior to 154), the information fraction equals 1.

With 154 or more primary endpoints with onset at least 28 days post vaccination at the time of database cutoff, the alpha-level for the secondary hypotheses is therefore 0.025 (2.5%). With, e.g., 77 primary endpoints, the information fraction equals 0.5 and the first secondary hypothesis is then evaluated at the alpha-level 0.0147. If this test is significant, the alpha will be passed on to the next hypothesis as specified in Figure 2.

Figure 2 Graphical approach for the hypothesis evaluation



[a] alpha level passed down to the secondary tests is based on a GSD with a single interim analysis and with information fraction determined by the primary endpoint including all events with onset at least 28 days post vaccination (i.e., number of primary events with onset at least 28 days post vaccination at the time of data base cut off (when the respective efficacy boundary is crossed by each co-primary endpoint and the data requirement are met) divided by the TNE) and corresponding alpha-level obtained from a Pocock boundary.

[b] If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached (8-week median follow-up timepoint), to support health authority interactions. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

[c] When testing the co-primary endpoints at the time of the snapshot analysis or at the time of the primary analysis, both will have to reach significance in order to continue with the hierarchical testing.

The hypothesis VE>0% will be tested based on calculations of a $(1-2\alpha^*)\%$ two sided CI, if the lower-limit then exceeds 0%, the hypothesis is rejected.

3. SAMPLE SIZE DETERMINATION

3.1. Efficacy (Total Sample Size)

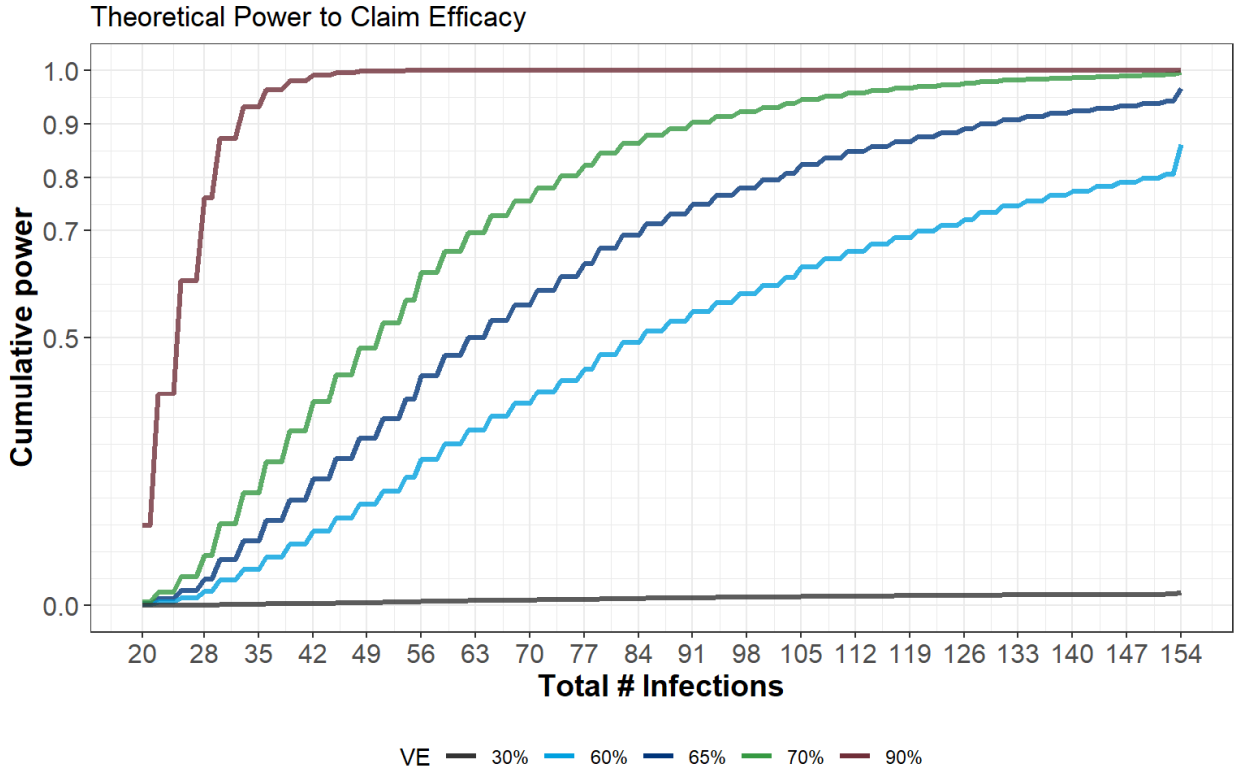
The study TNE is determined using the following assumptions:

1. a VE for molecularly confirmed, moderate to severe/critical SARS-CoV-2 infection of 60%.
2. approximately 90% power to reject a null hypothesis of H0: VE≤30%.
3. type 1 error rate α = 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 5.4.3.1).
4. a randomization ratio of 1:1 for active versus placebo

Events for the co-primary endpoints are defined as first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition in Section 5.2 in the PP population at least 14 days after vaccination (Day 15) and at least 28 days after vaccination (Day 29) with study vaccine.

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 154, based on events in the active vaccination and placebo groups, according to the primary endpoint case definition of moderate to severe/critical COVID-19 (Section 5.2). Using the SPRT until the TNE when starting from the 20th endpoint onwards will result in 86.22% power to reject H0 when VE1=60%. The overall type I error is controlled below 2.5% at 2.398% when VE0=30%. In Figure 3 the power of the testing strategy for VE1 equal to 60%, 65%, 70% and 90% is shown for a total number of endpoints from 20 to 154. From the graph, the overall study power equals 96.6% for an assumed VE=65%, and close to 100% for an assumed VE=70%.

Figure 3 Theoretical Power based on the Exact Binomial distribution for VE1 = 60%,65%,70% and 90%; and Type I error rate under VE0 = 30%



If the primary hypotheses 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 is specified in section 2. The FWER will be controlled at 2.5%.

Sample Size Justification

Based on epidemiological modeling for the targeted study countries, province/states of the various site locations, the annualized incidence of moderate to severe/critical COVID-19 cases meeting the primary endpoint definitions has been predicted to be 1.4% for the October-November timeframe. The estimate incorporates that real-world-evidence data and literature data only detected and reported a fraction of SARS-CoV-2 infections.

Furthermore, it includes that, based on literature and real-world-evidence data, only a fraction of all infections meets the moderate to severe/critical COVID-19 case definition and the fraction varies by age as well (increasing with higher ages). Moreover, projections for the selected study regions indicate that incidences will decline over time. Finally, seroprevalence rates are expected to vary between 5-15%.

For the purpose of sample size evaluation, an incidence assumption of moderate to severe/critical COVID-19 cases meeting the primary endpoint definition of 1.4% during the first 3 months of the

study, with a 50% reduction in Month 4, and 62% reduction in the months thereafter is assumed in combination with a seroprevalence rate of 10%.

The epidemiological situation will remain uncertain during the course of the study: actual seroprevalence rates, degree of social distancing and use of personal protective equipment during the study, local regulations (eg, potential lockdowns, other vaccines if available) potentially becoming in effect during the course of the study and potential drop-outs from the study may impact the disease incidence rate.

To that end, the maximum sample size of approximately 60,000 participants will be selected. This sample size is selected, based on 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 8 months of the study for a vaccine with an assumed 60% VE.

Based on an estimated case-hospitalization ratio of 2.5% and estimates obtained from reported real-world-evidence data of 3-10% of all SARS-CoV-2 infections meeting the severe/critical COVID-19 definition, this will provide a reasonable likelihood of observing 5 severe cases in the placebo group within the same time frame (8 months).

Added in Protocol Amendment 3: The incidence of moderate to severe/critical COVID-19 seen in the US and reported in other COVID-19 vaccine trials is significantly higher than assumed at the time of protocol planning. Epidemiological model-predictions indicate a range of 3.8% to 6.3% for Nov 2020 and 4.1% - 6.3% for Dec 2020. Furthermore, the ratio of non-severe versus severe events has been reported approximately 5:1 to 17:1 in other COVID-19 vaccine trials (Nov 2020). Employing these assumptions, modeling indicated there is a high probability that a signal of efficacy meeting the prespecified criteria in the Protocol Amendment 3 could be reached at or prior to the time when 50% of the participants will have been followed for a 8 weeks from the time of immunization, and therefore the sample size was reduced from 60,000 to approximately 40,000 participants.

3.2. Immunogenicity Subset

All participants included in the Immunogenicity Subset (N=400) will be added randomly at each stage of the staggered enrollment. Healthy adults (Subset 1a, n=100) will be enrolled in Stage 1a, adults with comorbidities (Subset 1b, n=100) in Stage 1b, healthy elderly (Subset 2a, n=100) in Stage 2a, and elderly with comorbidities (Subset 2b, n=100) in Stage 2b, with approximately 100 participants per group. The interactive web response system (IWRS) will be used to achieve these numbers and a 1:1 ratio between Ad26.COV2.S and placebo assignment within each Subset.

For 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 on Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year, 18 months, and 2 years after vaccination.

A sample size of 400 participants, is estimated to be sufficient to allow robust description of immune responses to Ad26.COV2.S vaccine. These numbers are expected to provide a robust

understanding of the magnitude and kinetics of the humoral response induced by the Ad26.COV2.S vaccine.

3.3. Immunogenicity Correlates (Correlates Subset)

Correlates will be assessed based on immune responses and transcriptome modifications measured in a random subcohort of vaccine recipients and in all vaccine recipients who experience a SARS-CoV-2 event (a primary endpoint or a secondary infection endpoint). Also, placebo participants will be included in this subset (placebo infected, seropositive [based on N-protein] non-infected and seronegative non-infected), if feasible. The goal of this case–cohort study is to assess correlates of risk of the primary endpoint and 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.

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

3.4. 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). Solicited AEs will be followed for 7 days, unsolicited AEs will be followed for 28 days.

3.5. Power calculations for other efficacy endpoints

3.5.1. Burden of disease endpoint

The statistical power associated with the BOD endpoint was evaluated under a range of scenarios for *VEmild* (30-50%) with *VEmod/sev=60%* and *a* relative incidence of mild events equal to 20%. The power values for the null hypothesis of *VE=0%* under these scenarios were all greater than 99% for the BOD endpoint (conditional on clearing the primary endpoint test and adjusted for multiplicity).

Table 2 below presents the simulation-derived Type I error rates for $H_0: VE_{BOD} = 0\%$ and $H_0: VE_{BOD} = 30\%$, (the latter included to match the null for the primary endpoint), assuming a relative incidence of mild infections of 20% and vaccine efficacy for moderate or severe/critical infections $VE_{mod/sev}$. Both controlled (using a Pocock boundary) and uncontrolled (passing down full alpha = 2.5% one-sided) values are reported.

The values of $VE_{\boldsymbol{mild}}$ in Table 2 are chosen to produce the required values of VE_{BOD} under the null hypotheses of VE equal to 30% and 0% respectively for each successive pair or rows. The large negative values of VE_{mild} required under some of the scenarios would in all likelihood be detected in the supplementary analysis planned for mild infections alone. It can be seen from Table 2 that the Type I error rate for the BOD secondary endpoint is well-controlled for both null hypotheses considered using a Pocock boundary based on a single interim analysis, but would be inflated if

an uncorrected one-sided alpha of 2.5% were used (though the inflation is relatively small, at most 1.4% for the scenarios considered).

Table 2 Type I error rates for BOD secondary endpoint tested at the time PA is triggered referring to H_0:〖VE〗_BOD=0% and H_0:〖VE〗_BOD=30%, using a 2.5% one-sided alpha (uncorrected) and a Pocock boundary. The relative incidences of mild and severe infections are both assumed to be 20%.

$VE_{mod/sev}$	H0:BOD	VE_{mild}	Pocock	Full alpha
30%	VE=30%	30%	0.016	0.018
	VE=0%	-150%	0.014	0.016
50%	VE=30%	-70%	**0.021**	**0.036**
	VE=0%	-250%	**0.021**	**0.039**
60%	VE=30%	-120%	**0.016**	**0.031**
	VE=0%	-300%	**0.015**	**0.028**
70%	VE=30%	-170%	0.012	0.025
	VE=0%	-350%	**0.016**	**0.031**

The simulations that produced the results in Table 2 were carried out using an event-based simulation engine. We allocate each event in a trial between the vaccine and placebo arms of the trial, and between mild, moderate and severe infections, using the categorical distribution. We compare the cumulative sums of moderate and severe events to the boundary to determine when boundary crossing occurs. We calculate the appropriate alpha level for secondary endpoint testing at the time of boundary crossing using a Pocock two-stage design, implemented using the gsDesign R package. The information fraction used is the number of moderate and severe events at the time of boundary crossing divided by the TNE. We compute the test statistic for the burden of disease endpoint using the formulas in Mehrotra et al. 2020. We simulate 10,000 trials for each scenario.

3.5.2. Medical intervention

The probability to reject the null hypothesis VE=0% for the endpoint medical intervention for a given one-sided significance level with 23 events is visualized in Table 3. This probability is approximately 85% for an assumed VE=80% and approximately 99% for an assumed VE=90%. Therefore a minimum of 23 events is deemed sufficient to ensure a reasonable power for the evaluation of the medical intervention endpoint.

Table 3 Probability to reject the null hypothesis VE=0 for the endpoint medical intervention for a given one-sided significance level with 23 observed medical intervention endpoints

Available alpha	Information fraction	Probability for 80%VE	Probability for 90% VE
0.0065	20/154	85%	99%
0.00665	30/154	85%	99%
0.0069	50/154	85%	99%

0.0079	100/154	85%	99%
0.0125	154/154	85%	99%

3.5.3. Asymptomatic infections and all infections (including asymptomatic)

The cases in the placebo group were assumed to be distributed as follows: 45% asymptomatic cases and 55% symptomatic cases of which 20% were mild infections, and 60% were moderate and 20% were severe infections, according to the case definitions. Based on a VE as detailed in Table 4, events were simulated according to a binomial distribution and the primary endpoints evaluated against the SPRT boundary.

Upon crossing the SPRT boundary, the power against asymptomatic or undetected infections as well as against the evaluation of all infections was calculated (null hypothesis VE>0). The alpha level for that evaluation was adjusted according to the procedure detailed in the statistical hypothesis evaluation.

The results are based on 1000 simulations. The powers presented are not conditional on passing the first 2 secondary hypotheses.

Table 4 Powers for Asymptomatic and All Infections for various Fractions of available N-Elisa samples at 2.5 months at the time of analysis

Fraction of available N-Elisa samples At 2.5 months	Vaccine efficacy			Power		
	Moderate/ Severe	Mild	Asympto-matic	Moderate/ Severe	Asympto-matic	All infections
100%	70%	60%	30%	99%	14%	96%
100%	70%	60%	40%	99%	28%	99%
100%	70%	60%	50%	99%	47%	>99%
50%	70%	60%	30%	99%	4%	99%
50%	70%	60%	40%	99%	7%	>99%
50%	70%	60%	50%	99%	13%	>99%

This is based on the protocol assumed incidence of 1.4% during 3 months and waning thereafter (by 50% in Month 4, by 62% in Month 5 and beyond) and a sample size of 60,000.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Vaccine assignment will be analyzed according to an as-treated principle. The analysis sets that are used for the various analyses are described in Table 5.

Table 5 Analysis Sets

Analysis Sets	Description
Enrolled	The enrolled analysis set includes all participants who signed the ICF and who were not screen failures
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	All randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment.
Per Protocol Efficacy Set (PP; primary efficacy analysis set for vaccination studies)	Participants in the FAS who received study vaccine and who were seronegative at the time of vaccination and who have no major protocol deviations that were judged to possibly impact the efficacy of the vaccine. See below for a definition.
Per Protocol Immunogenicity Analysis Set (PPI)	All randomized and vaccinated participants, including those who are part of the Immuno 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 Immuno 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.

For the PP the following additional criteria will be applied:

- having received the vaccine according to the randomization schedule
- having received at least 80% of the scheduled vaccination volume (according to the administration log)
- met inclusion criteria 1 (informed consent was obtained)

Some violations will not lead to exclusion of the subject from the PP, but data from the time-point of major protocol deviation onwards will be excluded from the analysis (if all data post-vaccination is excluded, the participant will be excluded from the PP):

- use of prohibited concomitant medications or medical conditions that were judged to probably impact the efficacy of the vaccine based on blinded medical review will be assessed on a case by case basis and documented before confirming a case for continuous monitoring or data base lock
- administration of another SARS-CoV-2 vaccine before or during the trial
- the participant became aware of the treatment code.

The following variables are relevant for in/exclusion of analyses:

- Seropositive or seronegative at baseline. A baseline serologic test for past or current infection with SARS-CoV-2 will be performed for all participants. Samples for the baseline serologic tests will be sent to the central lab for testing. Results will be categorized as positive or negative. If a participant is seropositive at baseline, the participant will be excluded from the PP set. In case the test result is missing or unknown the participant will be considered as seronegative for analysis purposes.
- PCR positive (PCR+) or negative (PCR-) at baseline: a sample for SARS-CoV-2 infection at baseline will be collected for each participant. For participants with a positive SARS-CoV-2 infection during the study this sample will be tested. If a participant was analyzed PCR+ at baseline, the participant will be excluded from the PP set. A missing value will be considered as PCR- for analysis purposes.

Timing of the infection: the onset of a symptomatic SARS-CoV-2 infection is defined in section 5.2. Based on the onset of infection, subjects will be included as

- For analysis with onset after vaccination: if onset occurred on or after Day 2 in the study (i.e. the Day after vaccination or beyond). At this stage there is however no expectation that the vaccination has achieved its full efficacy.
- For analysis with onset at least 14 days after vaccination: if onset occurred at or after Day 15. Subjects with an onset prior or at Day 14 will be excluded from the analysis.
- For analysis with onset at least 28 days after vaccination: if the onset occurred on Day 29 or beyond. Subjects with an onset prior or at Day 28 will be excluded from the analysis.

Analyses of safety will be performed on the FAS.

Analyses of efficacy will be performed on the PP population and will be repeated on the FAS.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless otherwise indicated, all analyses will pool data across ages and with/without co-morbidities for evaluation without stratification.

Analysis adjusting for randomization factors will be explicitly mentioned when done and will include the age groups and with/without co-morbidities only.

Stratification for (mobile) site unit at the time of randomization was done to ensure balance in exposure to SARS-CoV-2 between randomized groups over time because of the spatiotemporal evolution of the epidemic. However, including all stratification factors (age by comorbidity by (mobile) site) in the analysis will result in a large number of ‘empty strata’ (i.e. without cases) as the TNE of 154 is substantially lower than the anticipated number of stratification levels. Therefore no summaries will be provided by this stratification factor (mobile unit).

5.1.1. Study Phases

A baseline (or reference) value will be defined as the value of the last available assessment prior to the vaccination on Day 1.

The safety analysis will present all results by study phase (see Section 5.1.2). Immunogenicity results will be presented per scheduled time point as appropriate. Listings will be shown per phase and time point.

Study day or relative day is defined as follows:

- Study Day = visit date – date of Day 1 + 1; if visit date >= date of Day 1 (date of first vaccination).
- Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of first vaccination).

5.1.2. Phase Definitions

The phases in the study will be constructed as follows:

Table 6 Phase Definitions for Safety Analysis

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
Post-dose	2	Post-dose	1	Date and time of first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days)
Follow-up (D30-M6)	3			Day 30, 00:00	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) One minute prior to Month 6 (date of vaccination + 6 Months)
Follow-up (M6-W52)	4			Month 6, 00:00	Minimum of: a) 23:59 at the date of last contact (for early discontinuation)

					b) 23:59 at the date of data base cut-off date in case of interim c) One minute prior to Week 52 Visit
Long term Follow-up (W52-End)	5			Week 52 Visit	a) 23:59 at the date of data base cut-off date in case of interim Or maximum of: b) 23:59 at the date of last contact (for early discontinuation) c) 23:59 at the date of last visit

5.1.3. Unblinding due to availability of other authorized/approved COVID-19 vaccines

Investigators may receive requests to unblind study participants who become eligible to receive other COVID-19 vaccines if/when these are authorized/licensed for use. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for a 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 as 'availability of other COVID-19 vaccine'. The date(s) of administration of the other COVID-19 vaccine should be recorded.

When unblinding, if it is determined that the participant received the Janssen vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the schedule of activities to the extent that they permit. Safety evaluations will be identical for all participants, including participants that are unblinded to obtain another COVID-19 vaccine and who remain in the study, including participants in the safety subset, if applicable and feasible.

Subjects who were unblinded are censored at the time of unblinding for the evaluation of primary and secondary objectives. The data after unblinding of these unblinded participants will be analyzed separately for both safety and efficacy analysis.

5.2. COVID-19 case classification

Definitions relevant to COVID-19 case classification are listed below.

- **Episode** (of COVID-19): An episode of COVID-19 is defined as the period of the onset of (COVID-19) symptoms up until resolution of the episode. The severity of a COVID-19 will be determined based on the maximum severity observed across the episode.

- **Onset of (**COVID-19) **symptoms:** This is the date when any sign(s) or symptom(s) suggesting possible COVID-19. It will be called Day 1 of an episode. It is the date the first symptom of an episode entered on the eCOA or on the CRF if entered by the site ("*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).*" CTP). [Day 1 will be derived based on the first symptoms that are entered in the eCOA before the first swab is taken. In case there are multiple days with symptoms entered in the eCOA before the first swab, Day 1 is defined as the first Day of all consecutive Days with signs or symptom that are at least mild.]

- **Resolution of an episode:** 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. [The date taken will be the first of the 2 consecutive negative swabs, OR the first day with no COVID-19 related signs or symptoms, whichever comes last. For this determination, all sources of information will be used (eCOA, eCRF). In case of missing days, it will depend if those are before or after the first day of the two consecutive SARS-CoV-2 negative nasal swabs. If before days with missing data have no consequence. If after, it is assumed that if days with missing data are after a day with no symptoms, the subsequent days also were without symptoms. If days with missing data are after a Day with symptoms, the assumption depends on the data of subsequent Days. If there are no more than 2 Days without data and the next Day does have (at least mild) symptoms, the missing days will be assumed to also have had symptoms. In all other cases it will be assumed that days with missing data were without symptoms and the rule to determine the resolution of symptoms will be applied.]

- **Molecularly confirmed case:** Events for which at least one SARS-CoV-2 PCR positive test was obtained by the University of Washington central testing facility.

- **Analysis-ready** case: A case is considered *analysis-ready for efficacy monitoring* if it has a central SARS-CoV-2 positive test AND is considered cleaned at any point in the episode, at the latest on Day 15 (i.e., 14 days after onset). At this time it will be categorized as mild, moderate, severe/critical; and categorized according to the harmonized FDA definition (yes/no). Cases that have not resolved at or before Episode Day 15, will be categorized to the highest severity level reached at Episode Day 15. Statistical analysis against the monitoring boundaries will be performed on analysis-ready cases only (see Section 5.2).

- Case **not analysis-ready:** A case for which the SARS-CoV-2 test is positive, but the case has either not been cleaned and/or central confirmation not available before reaching Episode Day 15; categorization is *not considered analysis-ready*. The SSG will be provided with all analysis-ready and not analysis-ready cases (see Section 5.2). As the false-positive rate is low, for these cases also local SARS-CoV-2 PCR tests will be considered for cases not analysis-ready (but not for analysis-ready cases).

5.2.1. Assigning Case Definition

The case definitions for mild, moderate, and severe/critical COVID-19 are provided in the CTP Section 8.1.2. This section provides guidance on how these will be applied.

- Information on symptoms is to be collected from the eCOA (see Appendix 6 of the CTP) and from the eCRF entered by the site. In case the sources are inconsistent (i.e., on a single calendar Day one source records the symptom and another source does not record that same symptom) the symptom is considered to have been present on that Day.
- A sign or symptom is considered as absent or present for a COVID-19 episode: any sign or symptom is considered present if observed in the eCOA or eCRF for the COVID-19 episode, and absent if not.
- Signs or symptoms occurring at any time during the episode are used for the application of the case definitions.
- The application of the criteria is independent of duration; if a sign or symptom is present at any time, the sign or symptom is considered to be present. [Note that for a suspected COVID-19 case to be tested, at least one symptom of suspected COVID-19 has to be present for 24 hours, and not otherwise explained (Section 8.1.1. of the CTP: "New onset or worsening of any 1 of these symptoms, which lasts for at least 24 hours, not otherwise explained"). For case classification the information from the eCOA and eCRF is taken independent of duration or alternative explanations.]
- Fever will be assessed independent of method (oral, armpit, ear, or rectal).
- The definitions of *mild*, *moderate*, and *severe/critical* are mutually exclusive, where the most severe category takes priority.
- At the time of resolution of the COVID-19 episode, the collected information will be applied against the clinical case definition. For the purpose of continuous monitoring, the clinical case definition will be included as soon as analysis-ready independent of resolution (see above). In case symptoms worsen afterwards, increasing the classification of severity, the next continuous monitoring analysis will analyze the case according to the highest degree of severity at that time (see Section 5.9).
- All potential severe/critical COVID-19 cases defined as those cases that meet the severe/critical definition by scoring of signs and symptoms or meet the moderate endpoint definition with a total of 3 or more signs and symptoms will be assessed independently by a Clinical Severity Adjudication Committee (see Section 5.9.8). This committee will independently evaluate the severity of the COVID-19 cases in a blinded manner. Classification of the severe/critical designation in terms of severity will be based on the highest degree of severity during the observation period. Since this committee will evaluate case severity in a blinded manner it will be able to objectively evaluate moderate vs severe cases which will be its main priority.

For any case definition to be considered for classification of COVID-19 there needs to be at least one 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) that is confirmed by the central laboratory.

As there can be specific unforeseen situations where definitions as detailed in the SAP did not cover the specific situation, the Sponsor will at that time define additional data handling guidelines based on an assessment (blinded to treatment assignment) as close as possible to the intent of the rules as specified above. The Study Statistics and Programming team at the Sponsor will provide their additional data handling guideline to the SSG, which will be documented in the Data Presentation Specification document (DPS).

5.2.2. Symptomatic COVID-19 Case Derivation

Some symptoms lead to suspicion of a COVID-19 and are used as triggers to proceed with home-collection of the nasal swabs for SARS-CoV-2 testing as based on interaction of the participant with the site. The list of symptoms used as triggers for testing are provided in Section 8.1.1. of the CTP. A triggering symptom may lead to a (confirmed) positive SARS-CoV-2 test, where the case may fail to reach the mild case definition (or worse) at any time during the episode. These cases are not considered as symptomatic. In other words, symptomatic COVID-19 cases are those that are at least of mild severity as defined below.

Asymptomatic cases are defined as cases where a participant does not fulfil the criteria for mild, moderate or severe/critical COVID-19, and has a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample, OR develops a positive serology (non-S protein) test. In those cases the participant will be considered to have experienced asymptomatic or undetected COVID-19.

For any case to be considered a case at least one sample needs to have a SARS-CoV-2 positive RT-PCR from the central laboratory (University of Washington). The derivations for mild, moderate, and severe/critical are given below.

5.2.2.1. Mild COVID-19 Case Derivation

A case will be considered of mild COVID-19 severity if one (or more) of the following symptoms is observed, if not satisfying the definition of a moderate or severe/critical disease severity [black, terminology from eCOA or blue, terminology from the eCRF]:

- Fever (≥38.0°C or ≥100.4°F) or eCRF
- Sore throat / Sore throat
- Loss of appetite / Malaise
- Feeling generally unwell (run down) / Malaise
- Fatigue (tiredness) / Malaise
- Physical Weakness] / Malaise
- Headache / Headache
- Muscle aches/pains / Myalgia
- Diarrhea / Gastrointestinal Symptoms

- Vomiting / Gastrointestinal Symptoms
- Nausea / Gastrointestinal Symptoms
- Abdominal/stomach pain / Gastrointestinal Symptoms
- Cough / Cough
- Chest congestion (mucus in chest)
- Runny nose
- Wheezing
- Skin rash
- Eye irritation/discharge
- Chills
- Uncontrollable body shaking/shivering /Shaking chills or rigors
- Decreased sense of smell / Anosmia (olfactory or taste disorders)
- Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Red or bruised looking feet or toes / Chilblains/pernio (red or bruised looking feet or toes)

5.2.2.2. Moderate COVID-19 Case Derivation

For the definition of moderate COVID-19 severity there are two separate criteria, either if met would be sufficient to be considered as moderate (if not satisfying the criteria of severe/critical disease):

1. At least one **sign** or symptom (as derived from the Medically-attended COVID-19 Form (MA-COV) form or other CRF source *or eCOA*):

- Respiratory Rate ≥ 20 breaths/minute or vital signs CRF
- Abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level
- Clinical or radiologic evidence of pneumonia
- Radiologic evidence of DVT
- *Shortness of breath (difficulty breathing)*

OR

2. Two (or more) signs or symptoms from of the following (black, terminology from eCOA or blue, terminology from the eCRF):

- Highest temperature was ≥38.0 ºC or ≥100.4 ºF or CRF
- Heart rate ≥ 90 beats/minute or vital signs CRF
- Chills or Uncontrollable body shaking/shivering /Shaking chills or rigors

- Sore throat / Sore throat
- Cough / Cough
- At least one from [Loss of appetite, Feeling generally unwell (run down), Fatigue (tiredness), Physical Weakness] / Malaise
- Headache / Headache
- Muscle aches/pains / Myalgia
- At least one from [Diarrhea, Vomiting, Nausea, Abdominal/stomach pain] / Gastrointestinal Symptoms
- Decreased sense of smell or Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Red or bruised looking feet or toes / Chilblains/pernio (red or bruised looking feet or toes)

5.2.2.3. Severe/Critical COVID-19 Case Derivation

A case will be considered severe/critical if (black, terminology from the Medically-attended COVID-19 Form (MA-COV) or blue, terminology from the eCRF):

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg)
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal or hepatic dysfunction
- Numbness, tingling, or weakness face or limbs (neurologic dysfunction)
- Difficulty speaking or forming speech (neurologic dysfunction)
- Difficulty understanding speech (neurologic dysfunction)
- Feelings of confusion (neurologic dysfunction)
- Admission to the ICU (Medical Encounters eCRF)
- Death (SAE form)

In addition, severe/critical cases can be identified through the use of the following vital signs:

- SpO2 ≤ 93%
- Heart rate ≥125 beats/minute
- Respiratory Rate ≥30 breaths/minute

OR via an internal review of PCR positive cases in subjects who have an SAE form to verify whether they meet any of the components of the severe case definition as specified in the protocol. This internal review will include medications or supplemental oxygen that would indicate treatment of any of the conditions meeting the severe case definition.

All cases meeting the severe/critical criteria will be adjudicated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

All cases meeting the moderate case definition and that include >= 3 signs or symptoms from the list of signs or symptoms will be evaluated by the Clinical Severity Adjudication Committee to determine if the case is severe/critical in their judgement.

Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive and will be used in the primary analyses of severe COVID-19 cases. Cases that are reviewed by the Clinical Severity Adjudication Committee that are not considered severe/critical will be classified as a moderate case.

Cases identified through the MA-COV, vital signs or the internal review (see above) will be used in a sensitivity analysis.

5.2.2.4. US FDA Harmonized COVID-19 Case Derivation

A case will be considered satisfying the FDA harmonized COVID-19 case criteria if at least one of the following symptoms was recorded during a COVID-19 episode (black, terminology from eCOA or blue, terminology from the eCRF):

- Fever (≥38.0°C or ≥100.4°F) or CRF
- Cough / Cough
- Chills (or Uncontrollable body shaking/shivering) /Shaking chills or rigors
- Sore throat / Sore throat
- Shortness of breath (difficulty breathing)
- Fatigue (tiredness) / Malaise
- Muscle aches/pains / Myalgia
- Headache / Headache
- Decreased sense of smell / Anosmia (olfactory or taste disorders)
- Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Chest congestion (mucus in chest)
- Nasal congestion (stuffy nose)
- Runny nose

- Joint aches/pains
- Diarrhea / Gastrointestinal Symptoms
- Vomiting / Gastrointestinal Symptoms
- Nausea / Gastrointestinal Symptoms

The FDA harmonized COVID-19 case definition is independent of the case definition above, meaning that each subject with a case of molecularly confirmed COVID-19 is considered as an FDA harmonized case (yes/no), and considered as either a case of mild, moderate, or severe/critical case.

5.3. Participant Dispositions

Participant information will be shown for the full analysis set.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- participants screened
- participants screen failed (and main reason for screen failure)
- participants in the FAS
- participants in the PP
- participants in the FAS but not in the PP (and reasons for not being in the PP)
- participants vaccinated and not randomized
- participants randomized and not vaccinated
- participants vaccinated with incorrect treatment
- participants who discontinued study (and reasons for termination)

Also, the number of participants and percentage per phase will be tabulated.

5.4. Primary Endpoint(s) Analysis

5.4.1. Timepoint of primary analysis

The interim monitoring for the primary analysis can start as soon as the following conditions are met:

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

No interim evaluation will be done, until those conditions are fulfilled. Monitoring for efficacy will not start before the above conditions 1-3 are met.

The efficacy analysis will be triggered by either:

a) An interim evaluation if all prespecified efficacy boundaries have been met simultaneously at the same calendar timepoint OR if at least 154 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 are observed for events with onset at least 28 days after vaccination

AND

b) The above 3 conditions are met.

OR, alternatively,

If the prespecified non-efficacy has been met (evaluating events with start 14 days after vaccination) or when the harm boundary has been crossed. The decision rules for harm and non-efficacy are detailed in Section 5.8.

If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of the enrolled participants is reached, an additional analysis will be performed when that follow-up timepoint is reached. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

If more than 154 primary endpoints are observed for events with onset at least 28 days after vaccination before the 3 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.

5.4.2. Definition of Endpoint and Estimand

The co-primary endpoints are defined as a COVID-19 case meeting either the moderate or severe/critical case definition with onset at least 14 days post vaccination and with onset at least 28 days post vaccination as defined in Sections 5.2.2.2 and 5.2.2.3.

The other estimand attributes therefore are:

Population: Prior SARS-CoV-2-uninfected, adults ≥18 years with or without comorbidities for COVID-19

Endpoints:

- Confirmed symptomatic moderate to severe/critical COVID-19 infections with onset ≥14 days after study vaccination, as defined in section 8.1.3.1 of the protocol.
- Confirmed symptomatic moderate to severe/critical COVID-19 infections with onset ≥28 days after study vaccination, as defined in section 8.1.3.1 of the protocol.

Interventions: Ad26.COV.S2 5×10^{10} vp and placebo

Summary Measure: Vaccine Efficacy: 100 x (1-ratio of incidence vaccine/placebo)%

Intercurrent Events: None

Data handling for estimators: Subjects with major protocol deviations potentially impacting efficacy will be excluded from the analysis. Subjects with a positive serology test at baseline will be excluded from the analysis. Cases will be counted from Day 15 and Day 29 (depending on the co-primary endpoint) until and including the last available timepoint in the data base. Subjects with an event before Day 15 or Day 29 (depending on the co-primary endpoint) will be excluded from the analysis.

5.4.3. Analysis Methods

Vaccine efficacy and evaluation of the primary hypotheses will be done based on the truncated sequential probability ratio test (Section 5.4.3.1) in the per-protocol analysis set including seronegative subjects.

The pre-specified boundary to declare a significant result for each of the co-primary endpoints is based on a one-sided truncated SPRT, assuming approximately 90% power to detect a VE=60%, at a 2.5% one-sided significance, starting from the 20th COVID-19 case in the PP population that meets the primary endpoint definition, up and until the 154th case (value at which the testing is curtailed). The boundary is visualized in Figure 6 .

In case interim monitoring has started (i.e. because minimal data requirements 1-3 were met) and the total number of events at the time of the primary analysis exceeds the TNE, e.g. due to rapid accrual of events in the last week, the SPRT boundary will be extended until the observed total number of events, keeping the overall alpha below 2.5% one-sided. This is achieved by avoiding the truncation of the SPRT boundary at the TNE, distributing the remaining alpha across the overrun events, in such a way as to maximize the boundary at the observed total number of events.

The operational evaluation of this boundary is detailed later in this section. As soon as this prespecified boundary has been crossed for both co-primary endpoints together with the second efficacy criterion related to the severe infections (simultaneously at the same calendar timepoint) and the other data requirements have been met, the primary hypotheses of vaccine efficacy (VE) against moderate to severe infections in the PP set: H_0: VE $\leq$30% versus H_1: VE >30% will be established.

To evaluate whether the second efficacy criterion has been met, the VE against severe infections will be calculated, as soon as the primary endpoints contain a subset of 5 severe events for each of the co-primary endpoints. If the point estimate VE >= 50% AND a minimum of 5 cases observed in the placebo group for both co-primary endpoints, this criterion is considered to be met.

Vaccine efficacy and the associated adjusted 100% (1-2α*) - confidence interval will be estimated as referenced in Appendix 8.

The primary analysis will be supplemented with subgroup analyses for age group (18 to <60 years, ≥60 years) and presence of comorbidities (yes/no) employing a descriptive summary including (unadjusted) 95% confidence intervals to describe the VE in each subpopulation using the same methods. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (≥70 years, ≥80 years). No hypothesis testing will be performed in these subgroups.

5.4.3.1. Sequential Probability Ratio Test

Using a similar notation of Dragalin et al. (2002) and Dragalin and Fedorov (2006) consider, X_1 and X_2 the number of events in the placebo group and the vaccine group, respectively. 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 $T = X_1 + X_2 =$ 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 $H1: \pi = \pi^*$using the conditional binomial test.

Consider $\alpha = P(reject\ H0 | VE = VE_0)$ 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, the TNE 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. Under the assumptions stated in Section 3.1, this formula suggests a TNE of T^*=154.

The implemented critical boundaries for success (Section 5.9.5) are based on the truncated SPRT (cfr. Jennison and Turnbull, 2000, chapter 12) 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. These boundaries are created by comparing the Likelihood Ratio of observing X_2 out of T endpoints under $H1$ vs. $H0$, using the above-mentioned exact binomial distribution. If the log-likelihood ratio is larger or equal to $ln(1 - \beta)/\alpha$ then H1 is concluded.

5.4.4. Operational implementation of SPRT and analysis in case of overrun

Based on modeling and simulation to minimize the risk of inconsistency and operationally to increase consistency in case evaluation, the evaluation whether or not the efficacy boundary has been crossed will be done on at least a weekly basis.

The boundary will be evaluated based on the available cases i.e., a COVID-19 episode that has been molecularly confirmed and analysis-ready according to the severity scale. The COVID-19 may still be ongoing.

1. At least every week, the available analysis-ready cases for efficacy monitoring will be evaluated against the primary endpoint definition and analysis population.

2. Based on the total number of analysis-ready cases and the vaccine:placebo ratio, the SSG will evaluate against the prespecified boundary whether the primary hypothesis has been rejected.

3. In case of rejection, the DSMB will provide the recommendation to proceed to the primary analysis to the Governance Committee upon which a decision can be implemented.

When the required 8-week follow-up after vaccination of 50% of participants is reached and when the decision is reached to proceed to analysis, the database cut-off date will be set to the date of the analysis when both boundaries are crossed and data requirements have been met. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of enrolled participants is reached, an additional analysis will be performed when that follow-up timepoint is reached. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

The primary analysis will be based on the cases of COVID-19 that were analysis-ready at this database cut-off date. The analysis of the secondary endpoints will include all analysis ready and resolved cases at the time of database lock.

This analysis will be supplemented with an analysis including cases that were not analysis-ready at the time of database lock, irrespective of whether a confirmed positive central reading was available for any sample taken before the time of the database lock. Those cases will be classified using the most severe classification during the episode available at the time of the locked database. The alpha level for the confidence interval and associated p-value will be based on the corresponding alpha level when the boundary was crossed.

For the operating characteristics of the SPRT and the statistical considerations justifying the practical implementation, the reader is referred to the modeling and simulation report.

5.4.5. Supportive analyses

The primary analysis will be supplemented with the following analyses.

For subjects with molecularly confirmed COVID-19, the follow-up time is defined as the time between vaccination and the time of onset of the case. For all subjects without COVID-19, follow-up time is defined as the time since vaccination until the last available measurement (for subjects ongoing in the study) or study discontinuation/completion.

Time to first occurrence of molecularly confirmed moderate or severe/critically ill COVID-19 is defined as the time between vaccination until onset of the case for the PP set. Subjects without moderate and severe/critically ill COVID-19 are censored at their follow-up time as defined above.

Subjects who were unblinded are censored at the time of unblinding for the evaluation of primary and secondary objectives. The data after unblinding of these unblinded participants will be analyzed separately for both safety and efficacy analysis.

In a supportive analysis of the primary efficacy endpoint, vaccine efficacy will be estimated with an associated two-sided confidence interval (Wald test) based on the hazard ratio obtained from a Cox proportional hazards regression model. The analysis will be stratified for age (>=60 yrs, <60 yrs) and comorbidities (with or without comorbidities). The strata will be based on the values in the database (which may differ to the strata as recorded in IWRS). The alpha-level at the time of crossing the boundary will be used to calculate the confidence interval.

As a supplementary analysis, a Negative Binomial model (using an asymptotic model including estimation of a dispersion parameter) will also be fitted.

The primary and supportive analysis as described for moderate and severe/critically ill COVID-19 cases in the per-protocol population in seronegative subjects will be repeated using the following analysis populations and endpoints:

- FAS, SN (seronegative) with onset of molecularly confirmed, moderate and severe/critically ill COVID-19 one day after vaccination
- PP, SN subjects with onset of molecularly confirmed, moderate and severe/critically ill COVID-19, at least 28 days after vaccination, thereby excluding subjects who were seropositive at or before Day 29 based on PCR or serological testing of Day 29 (subjects with missing data will be included)

The primary efficacy and supportive analyses will be repeated regardless of serostatus, if > 6 moderate and severe/critically ill COVID-19 cases were observed in seropositive subjects.

5.4.6. Sensitivity analyses

In case of potential waning VE over time the cumulative incidence vaccine efficacy against moderate or severe/critical COVID-19 with onset at least 14 days post vaccination and with onset at least 28 days post vaccination will be evaluated in the PP set, where all participants were seronegative at the time of vaccination. The method of Zeng (2004) will be used to estimate the cumulative incidence functions within each intervention arm, and pointwise two-sided Wald-based 95% confidence intervals for a log-transformed cumulative incidence ratio estimate will be provided over time. These intervals will be transformed to yield intervals for the cumulative incidence VE.

To evaluate the sensitivity to potential differential exclusion of major per-protocol deviations in the primary estimand, the following causal inference methods may be used. The efficacy will be estimated marginally among all participants who were seronegative at the time of vaccination in the full analysis set (FAS-SN). Longitudinal causal inference methods will be used to formally define this efficacy estimand. In particular, having major protocol deviations will be treated as a time-varying intervention and the estimand is defined as efficacy in the counterfactual world where no participants have a major protocol deviation and no participants are lost to follow-up (Robins,

1986). Methods for estimating this quantity make use of data from all participants in the FAS-SN cohort, including those who, in fact, do not belong to the PP set. For the causal estimand to be learnable from the data available, these methods require that time-varying covariates are available such that, at any given time, whether or not a person has yet had a major protocol deviation or has been lost to follow-up is independent of whether or not the person would have subsequently experienced moderate to severe COVID-19 in the scenario where, possibly contrary to fact, that person had not yet had a major protocol deviation or been lost to follow-up. Covariates to be considered include demographics, clinical participant characteristics, and clinic-level information.

A sequentially doubly robust targeted minimum loss-based estimator (TMLE) will be used to estimate the aforementioned causal efficacy estimand (see Algorithm 1 in Luedtke, 2017; see also van der Laan and Gruber, 2012). This TMLE has been shown to be more robust than alternative methods for estimating longitudinal causal effects (e.g., Bang and Robins, 2005 and van der Laan and Gruber, 2012). The TMLE that we will use is designed for a setting where time is discrete, and its performance guarantees rely on the number of time points not being too large relative to the sample size. Therefore, to properly account for the fact that moderate to severe COVID-19 is measured on a daily scale, the TMLE will be run with time discretized into two-week windows, and then the fact that events are measured on a finer scale will be accounted for by incorporating inverse probability of censoring weights into the estimation procedure.

The resulting TMLE requires an estimate of the probability of experiencing moderate and or severe COVID-19 by the start of each two-week period considered, conditionally on time-varying covariates and intervention arm. Similarly, the TMLE also requires the probability experiencing a composite censoring event by the start of each of these two-week periods, conditionally on these same variables, where this composite censoring event is defined as either having a major protocol deviation or being lost to follow-up. Both of these estimates will be obtained using the ensemble method superlearner (van der Laan, Polley, and Hubbard 2007) with logistic regression, using the cross-entropy loss function and 5-fold cross-validation. Superlearner selects an optimal weighted combination of the predictions from a collection of candidate regression algorithms, such as those based on generalized linear models or random forests. Each superlearner will be supplied with the following library of learners: SL.mean, SL.step, SL.bayesglm, SL.glm, SL.glm.interaction, SL.glmnet, SL.earth, SL.xgboost, SL.ranger. Inverse probability of censoring weights will be obtained using a Kaplan-Meier estimator for the time to the composite censoring event, conditionally on being at risk at the beginning of the given two-week window. A 95%-level Wald-type confidence interval will be developed for the log-transformed cumulative incidence ratio, and will then be transformed to yield a confidence interval for the vaccine efficacy.

5.4.7. Tabulations and Graphical displays

The time to onset of the first occurrence of molecularly confirmed COVID-19 (definition in section 5.2.2) will be graphically summarized using Kaplan-Meier methods for the following subgroups:

For moderate or severe/critical COVID-19,

- PP, seronegative subjects only with onset at least 14 days and at least 28 days after vaccination (co-primary endpoints)
- FAS, seronegative subjects only with onset 1 day after vaccination
- FAS, seronegative and seropositive subjects with onset 1 day after vaccination

*Note that in the PP there are no baseline-seropositive subjects – this population is defined as subjects who are baseline-seropositive and otherwise comply with the PP analysis set definition (e.g. no major protocol deviations).

These graphs will be summarized combined as well as for each type of infection separately (moderate or severe/critically ill COVID-19).

Furthermore, the number of events and incidence for each endpoint and population (#of events/#person-years of follow-up) will be tabulated by randomized group. For the tabulations regardless of serostatus, cases will be additionally summarized by serostatus at baseline and combined.

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%] with the method of Parzen, Wei and Ying applied to estimate pointwise and simultaneous $(1-\alpha)\times 100\%$ CIs.

Any subgroup analysis for VE will also be visualized with forest plots.

5.5. Secondary Endpoint(s) Analysis

5.5.1. Tabulations and graphical displays

The time to onset of the first occurrence of molecularly confirmed COVID-19 will be graphically summarized using Kaplan-Meier methods for the following analysis populations following subgroups:

- PP, seronegative subjects only with onset at least 14 days and at least 28 days after vaccination
- FAS, seronegative subjects only with onset 1 day after vaccination
- FAS, seronegative and seropositive subjects with onset 1 day after vaccination

*Note that in the PP there are no baseline-seropositive subjects – this population is defined as subjects who are baseline-seropositive and otherwise comply with the PP analysis set definition (e.g. no major protocol deviations).

These graphs will be prepared regardless of severity according to the case definitions mild, moderate and severe and for the US FDA harmonized case definition. Furthermore, the graph will be prepared by severity (for mild COVID-19 only, COVID-19 requiring medical intervention).

The number of events and event rate for each endpoint and population (#of events/#person-years of follow-up) will be tabulated by randomized group.

Unless otherwise indicated, follow-up time for each subject is defined as time since vaccination until onset of a COVID-19 episode or the last available study measurement (For subjects without a COVID-19 episode).

Any subgroup analysis for VE will be visualized as well with forest plots.

5.5.2. Key Confirmatory Secondary Endpoint(s) and Estimand(s)

5.5.2.1. Definition of Endpoint(s)

Endpoint Label	Endpoint definition
Any symptomatic infection (BOD)	For all subjects with a symptomatic, molecularly confirmed COVID-19 episode, classification based on any severity will be included. Weight-adjusted analysis for severe disease will be done as follows. Any case of mild or moderate COVID-19 will be given a score of 1, severe/critical COVID-19 cases will be given a score of 2. Subjects without a symptomatic, molecularly confirmed COVID-19 episode are implicitly categorized as 0.
Asymptomatic or undetected infection	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. **Serologic conversion** is based on the available data from Day 71 Month 6 or Month 12. If positive at any timepoint while the subject was seronegative at baseline and at Day 29, a subject is considered seroconverted. This endpoint will only be tested when all subjects have completed the 6 months timepoint. If Day 29 is missing or not available, then the subject is considered negative. Asymptomatic infections between Day 1 and Day 29 will also be analyzed as a supportive endpoint. If positive at Day 29, while the subject was seronegative at baseline, a subject is considered seroconverted.
All infections (Any SARS-CoV-2 Infection)	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 28 days after vaccination with study vaccine.

Severe/critical infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting severe/critical definition with onset at least 14 days and at least 28 days post vaccination.
COVID-19 requiring Medical intervention	First occurrence of COVID-19 requiring medical intervention defined requiring a: Hospitalization ICU admission mechanical ventilation ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) or linked to any molecularly confirmed, COVID-19 during a COVID-19 episode with onset at least 14 days and at least 28 days post vaccination

The confirmatory estimands therefore are

Population: Prior SARS-CoV-2-uninfected, adults ≥18 years with or without comorbidities for COVID-19

Endpoint: as defined above.

Interventions: Ad26.COV.S2 $5x10^{10}$ virus particles and placebo

Summary Measure: Vaccine Efficacy: 100x(1-ratio of endpoint mean vaccine/placebo)%

Intercurrent Events: /

Data handling for estimator: Subjects with major protocol deviations potentially impacting efficacy will be excluded from the analysis. Subjects with a positive serology test at baseline will be excluded from the analysis.

For the secondary endpoints all available cases at the time of data base cut off will be included in the analysis according to the pre-specified analysis population and time window for endpoint calculation.

The populations for analysis for the secondary endpoints are presented in Table 7.

Table 7 Key confirmatory secondary endpoints and analysis set evaluations

	Key analysis population for evaluation of the statistical hypothesis	Supportive analysis set
Any symptomatic infection (BOD)	Per-Protocol analysis set baseline-Sero-Negative subjects with onset of infection at least 14	PP, SN/SP, Day 28* FAS, SN, Day 1 FAS, SN/SP, Day 1*

	days and at least 28 days post vaccination	
Any SARS-CoV-2 infection	Per-Protocol analysis set Sero-Negative subjects with onset of infection at least 28 day post vaccination	FAS, SN, Day 1 FAS, SN/SP, Day 1* PP, SN/SP, Day 28
Severe infection	Per-Protocol analysis set Sero-Negative subjects with onset of infection at least 14 and at least 28 days post vaccination	PP, SN/SP, Day 28* FAS, SN, Day 1 FAS, SN/SP, Day 1*
Medical intervention	Per-Protocol analysis set Sero-Negative subjects with onset of infection at least 14 and at least28 days post vaccination	PP, SN/SP, Day 28* FAS, SN, Day 1 FAS, SN/SP, Day 1*
Asymptomatic or undetected infection	Per-Protocol analysis set Sero-Negative subjects with onset at least 28 days post vaccination	FAS, SN Day 1
Asymptomatic or undetected infection from Day 1 to Day 29	FAS, SN Day 1	
PP=per-protocol, SN=sero-negative subjects, Day 1/28=including infections with onset 1 day/28 days post vaccination, SP=seropositive subjects, FAS=full analysis set (*)Any analysis regardless of serostatus will be done only if 7 or more events observed in the group of subjects who were seropositive at baseline.		

5.5.3. Supportive Secondary Endpoint(s)

To understand and characterize the vaccine efficacy against any symptomatic infection, as well as under any infection, the following supportive endpoints will be supplemented with the confirmatory secondary endpoints.

The evaluation of secondary endpoints will be done in the per-protocol analysis set in seronegative subjects, with onset at least 14 and at least 28 days after vaccination. All analyses will be repeated regardless of serostatus.

	Endpoint definition
Mild infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting mild definition with onset at least 14 and at least 28 days post vaccination.
Moderate infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting moderate definition with onset at least 14 and at least 28 days post vaccination.
US FDA Harmonized COVID-19 cases	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting the US FDA harmonized case definition with onset at least 14 and at least 28 days post vaccination
Viral Load AUC (VL-AUC)	Area under the viral load-time curve (VL-AUC in $\log_{10}$ copies/ml) of SARS-CoV-2 viral RNA load as determined by quantitative RT-PCR assay of nasal available samples during the COVID-19 episode.

	Nasal swab samples are taken at the start of the COVID-19 episode and every 2 days thereafter for the next 14 days or until 2 consecutive negative swabs, whichever occurs later. VL-AUC is calculated based on the viral load values until resolution of the COVID-19 episode. In the calculation of the AUC, all available information (date, timing in hours, and minutes as captured in the data base will be used, but the AUC result will be reported in hours), of the assessment, is taken into account. Data handling regarding the following will be added to the Data Presentation Specifications (DPS): • PCR local lab versus central lab data • saliva • handling of values below LLOQ/LLOD $$\text{AUC VL} = \sum_{i=2}^{T} \frac{[VL_{t_i} + VL_{t_{(i-1)}}]}{2} [t_i - t_{(i-1)}]$$ where $\mathbf{t_i = (actual)\ timepoint\ i}$ $\mathbf{t_{i-1} = (actual)\ timepoint\ (i-1)}$ $\boldsymbol{T = last\ timepoint}$ $\mathbf{t_1 = first\ timepoint}$ $\mathbf{VL_{t_i} = log_{10}\ viral\ load\ at\ (actual)\ timepoint\ i}$ $\mathbf{VL_{t_{(i-1)}} = log_{10}\ viral\ load\ at\ (actual)\ timepoint\ (i-1)}$ This will be calculated for all subjects with a molecularly confirmed infection.

5.5.4. Analysis Methods

5.5.4.1. VE against severe/critical infection with onset at least 14 and at least 28 days after vaccination

The VE will be estimated with an associated adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0%, the lower-limit of the adjusted confidence interval will be

compared to 0, the hypothesis of moderate to severe infection with onset at least 14 and at least 28 days after vaccination will be rejected if the lower limit of the confidence interval is > 0%.

5.5.4.2. VE against any symptomatic infection – burden of disease

To evaluate the vaccine efficacy against any symptomatic infection, the severity-adjusted vaccine efficacy VE_{BOD} will be calculated based on BOD as follows. This vaccine efficacy measure is equal to the percent reduction in mean BOD score in the vaccine arm relative to that in the placebo arm.

Letting p_1 and p_2 denote, respectively the relative incidence of mild and moderate infections among symptomatic infections, and VE_1, VE_2, VE_3 represent, respectively, the vaccine efficacy for mild, moderate and severe/critical infections, the vaccine efficacy for BOD, under 1:1 allocation for vaccine and placebo, can be expressed as

$$VE_{BOD} = 1 - \left[(1 - VE_1)p_1 + (1 - VE_2)p_2 + 2(1 - VE_3)\big(1 - (p_1 + p_2)\big)\right] / \big(2 - (p_1 + p_2)\big)$$

Letting $BOD_V(n)$ and $BOD_P(n)$ represent the sums of the BOD scores for (symptomatic) infections in the vaccinated and placebo arms, respectively, then the estimated vaccine efficacy for the BOD endpoint after n infections (under equal allocation to vaccine and placebo) is $\widehat{VE}_{BOD}(n) = 1 - BOD_V(n)/BOD_P(n)$. An expression for an (asymptotic) lower confidence bound for VE_{BOD} based on $\widehat{VE}_{BOD}(n)$ is provided in (supplementary appendix, Mehrotra et al, 2020). The alpha* - level of the confidence interval will be compared against 0.

This lower bound will be compared against 0% to evaluate the study hypothesis against any symptomatic infection according to the statistical testing strategy specified in section 2.

In addition, the vaccine efficacy will be estimated with an associated unadjusted confidence interval for each severity separately (mild, moderate, severe/critical) according to the case definition.

Estimators for VE1, VE2 and VE3 in the PP-SN, together with their 95% CIs, are presented in Appendix 8.

5.5.4.3. Any SARS-CoV-2 infections and asymptomatic infections

The proportion of subjects (out of subjects with available measurements) who serologically converted will be graphically visualized and tabulated at every available timepoint by randomized group, together with the number of subjects with an available measurement.

Additional tabulation will summarize the number of subjects with and without a SARS-CoV-2 infection as having

1. Not infected

2. Asymptomatic or undetected subjects
3. Symptomatic molecularly confirmed, with mild COVID-19
4. Symptomatic molecularly confirmed, with moderate COVID-19
5. Symptomatic molecularly confirmed, with severe COVID-19

A subject will be classified based on their worst occurrence and in one category only.

All subjects with multiple SARS-CoV-2 molecularly confirmed infections during the study will be tabulated by severity and vaccination group in the FAS-SN as well as SP set.

To assess the effect of Ad26.COV2.S on occurrence of any infection with SARS-CoV-2 as compared to placebo, VE will be estimated with an associated 95% confidence interval. If the timepoint of hypothesis testing is reached (when at least 15,000 subjects with a Day 71 available sample), adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0, the lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of protection against infection will be rejected.

To understand the vaccine efficacy of Ad26.COV2.S on occurrence of asymptomatic or undetected infections with SARS-CoV-2 alone, as compared to placebo, the VE will be estimated with a 95% confidence interval. If the timepoint of confirmatory testing is reached (when all participants have at least 6 months of follow-up), an associated adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0, the lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of protection against infection will be rejected.

For cases, the follow-up time is defined as the time between vaccination and the time of onset of infection (timepoint of a positive N-protein Elisa for asymptomatic subjects).

5.5.4.4. Medical intervention

Vaccine efficacy will be summarized with a 95% confidence interval (methods in Appendix 8)

When sufficient number of events are observed, an adjusted confidence interval will be calculated with the alpha-level α* derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0%, the lower-limit of the adjusted confidence interval will be compared to 0%, the hypothesis of protection on medical intervention endpoints will be rejected if the lower limit of the confidence interval is > 0%.

For cases, the follow-up time is defined as the time between vaccination and the onset of the first event (according to the considered endpoint), for non-cases, it is the time between vaccination and data base cut off date (for subjects ongoing) or study discontinuation.

5.5.4.5. AUC viral load

To compare VL-AUC after infection between the active and placebo groups, the exact Wilcoxon Rank Sum test will be performed.

For the primary analysis, values below the LLOQ (indicated as 'Not Quantifiable' in the data base) will be imputed with 0. At the time of the final analysis, the same analysis will be repeated, so values below the LLOQ (indicated as 'Detected' or 'Not Detected') will be imputed with 0.

These imputations will be used when calculating the AUC based on equation (1). In addition, in case some observations are missing at the first timepoint after infection and/ or the last timepoint after challenge, missing values should be imputed with 0. No other missing values will be imputed.

AUC-VL values will be descriptively summarized (mean, median, SD, SE, range) by randomized group and COVID-19 severity (all symptomatic infections, mild, moderate to severe/critical). Individual profiles of viral load over time and log10[viral load] over time since onset of a COVID-19 episode will be summarized by randomized group and severity of COVID-19.

The vaccine efficacy against AUC-VL will be estimated through the geometric mean ratio of AUC-VL with associated 95% confidence interval.

As the comparison of the AUC VL after infection between the active and placebo groups is based on post-randomization groups, this analysis may not assess the causal effect of the vaccine on viral load. A sensitivity analysis as described by Gilbert et al. (2003) will be carried out. In this sensitivity analysis, a logistic selection bias model is employed to define a causal estimator for the vaccine effect on viral load. The unknow slope (b) of this logistic model determines the amount of selection bias; b is varied over a plausible range of values. For each value of b, a non-parametric estimate of the causal vaccine effect is calculated. A confidence interval and p-values for the appropriate hypothesis of interest are obtained by bootstrap. If $b<0$, there is a selection bias towards a lower viral load in the vaccine group as compared to the placebo group. When $b=0$, no selection bias is assumed. The hypothesis of interest is the one-sided hypothesis of a reduction of the viral load. Therefore, values of $b \leq 0$ will be considered (from -5 to 0 in steps of 0.01). The estimate of the causal vaccine effect with its 100*(1-2*alpha) % confidence interval and the p-value for the one-sided hypothesis of a viral load reduction in the vaccine group will be plotted against the assumed value of b.

The analysis will be carried using R-code developed by P.N. Gilbert and R.J. Bosch. Number of bootstrap samples will be set to 10000 to achieve adequate precision for the derived p-values. The seed will be fixed to allow reproducibility of the result.

5.5.4.6. US FDA Harmonized definition

Estimating the Vaccine Efficacy (*VE*) and the associated confidence interval for the US FDA harmonized definition will be done according to the methodology as explained in Appendix 8.

5.5.4.7. Mild Cases

Estimating the Vaccine Efficacy (*VE*) and the associated confidence interval for participants with an infection that is at most of mild severity will be done according to the methodology as explained in Appendix 8.

5.6. Tertiary/Exploratory Endpoint(s) Analysis

The potential association between vaccine efficacy and baseline or other potential influential factors (including but not limited to region, age group, comorbidities, Ad26 VNA seropositivity, SARS-CoV-2 seropositivity, profession, smoking status, seropositivity against other coronaviruses and coinfection with any other respiratory pathogens and other risk factors) will be explored by multivariate, covariate-adjusted analyses or subgroup summaries.

All exploratory endpoints analysis will occur in the PP analysis set, in seronegative subjects unless otherwise indicated.

Other ad hoc analyses may be performed if deemed appropriate to characterize the safety, immunogenicity and efficacy profile of the vaccine. Post-hoc analyses (analyses performed that are different from this SAP) that are included in the final CSR will be documented in the Changes to Planned Analyses section of the CSR.

5.6.1.1. Definition of Endpoint(s)

Endpoint	Endpoint definition
Time to SARS-CoV-2 virus no longer detectable	A subject is considered as having an infection if the case is classified as mild, moderate or severe. For each subject the time to "SARS-CoV-2 virus no longer detectable" is the time between the onset of the COVID-19 episode and the first sample that is negative and after which no positive sample was observed. For this assessment only centrally confirmed assessments will be taken into account. The precision of this difference will be in Days, defined as the Day of the episode where this criterion is met (e.g., if the first sample that was negative was on Day 12 of the episode, the time to no longer detectable will be set at 12 Days.
Peak viral load	A subject is considered as having an infection if the case is classified as mild, moderate or severe. The peak viral load is defined as the highest viral load that was observed during a COVID-19 episode. For this assessment only centrally confirmed assessments will be taken into account.
Viral load over time	A subject is considered as having an infection if the case is classified as mild, moderate or severe. For this assessment only centrally confirmed assessments will be taken into account. For each assessment the viral load will be categorized to the two day schedule, where the first value will define the series. If a viral load is available before and after a scheduled day, the average on the $\log_{10}$ scale will

	be used. If only one value is available in an adjacent day this value will be used.

The additional endpoints on viral load by quantitative RT-PCR are defined above and will be analyzed descriptively for all symptomatic cases separately by severity (all symptomatic infections, mild, moderate to severe/critical).

Assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo by first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) from Day 1 to Day 29.

First occurrence of any health care utilization linked to any molecularly confirmed COVID-19. Health care utilization is defined as any event such as hospitalization, ICU admission, ventilator use linked to any molecularly confirmed COVID-19 at least 14 days and 28 days post-vaccination.

Assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection in participants with comorbidities associated with increased risk of progression to severe COVID-19, as compared to placebo defined as first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) in participants with comorbidities associated with increased risk of progression to severe COVID-19 with onset at least 28 days after vaccination with study vaccine.

To explore the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not previously described, as compared to placebo by first occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days and at least 28 days after vaccination with study vaccine.

To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo by deaths occurring at least 14 days and at least 28 days after vaccination with study vaccine.

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 by assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), 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 for 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, adenovirus neutralization as measured by VNA, analysis of antibodies to S and the receptor-binding domain (RBD) of the SARS-CoV-2 S protein and SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type virus and/or pseudovirion expressing SARS CoV-2 S protein).

To explore changes in the SARS-CoV-2 genome by 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 by presence, severity and duration of COVID-19 signs and symptoms and 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 by reduction in severity of COVID-19 signs and Symptoms

To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity.

To assess the incidence of co-infection of COVID-19 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.

To assess the frailty index in participants who received Ad26.COV2.S as compared to placebo.

5.6.1.2. Analysis Methods

For the assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed, mild COVID-19 by serial viral load measurements during the course of a COVID-19 episode the analysis method as described in section 5.5.4.5 will be repeated limited to the molecularly confirmed, mild COVID-19 cases.

For the first occurrence of any health care utilization linked to any molecularly confirmed COVID-19 defined as any event such as hospitalization, ICU admission, ventilator use linked to any molecularly confirmed COVID-19 at least 14 days and 28 days post-vaccination, the proportion of participants will be tabulated and an exact Poisson model will be performed. The ratio of incidence densities (IDR) will be computed for the vaccine versus placebo with the 95% exact CIs together with the percent reduction in health care utilization defined as 100*(1-IDR). If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) will be investigated. If enough cases per event type are available (more than 6) a separate model can be performed per event type.

For the assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo by first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) with onset at least 28 days after vaccination with study vaccine the analysis method as described in section 5.3 will be repeated using all SARS-CoV-2 infections. This analysis will be done using the PP and will be repeated in the FAS for participants with comorbidities associated with increased risk of progression to severe COVID-19 (as defined by the CDC, section 6.7).

For the assessment of the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not

previously described, as compared to placebo by first occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days and at least 28 days after vaccination with study vaccine the proportion of participants will be tabulated and an exact Poisson model will be performed. The ratio of incidence densities (IDR) will be computed for the vaccine versus placebo with the 95% exact CIs together with the percent reduction in respiratory disease defined as 100*(1-IDR). If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) will be investigated.

For the assessment of the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo by deaths occurring at least 14 days and at least 28 days after vaccination with study vaccine, the proportion of participants will be tabulated and an exact Poisson model will be performed. The ratio of incidence densities (IDR) will be computed for the vaccine versus placebo with the 95% exact CIs together with the percent reduction in deaths defined as 100*(1-IDR). If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) and age group. All-cause deaths occurring will be summarized by Kaplan-Meier method, and KM plot will be provided.

For the evaluation of 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 by assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), with the risk of COVID-19 and protection induced by the study vaccine participants with a COVID-19 episode immunogenicity data will be tabulated by vaccine regimen at baseline, 28 days post vaccination, on COVID-19 Day 3-5 and on COVID-19 Day 29 for the standard immunogenicity assays (S-ELISA and VNA) and on COVID-19 Day 3-5 and on COVID-19 Day 29 for all other assays that are available (Table 8). Immunogenicity data will be graphically displayed by vaccine regimen where actual values are shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay. 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. These analyses will be described in a separate correlates SAP for this purpose.

For the assessment of the humoral immune response to Ad26.COV2.S, as compared to placebo for 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, adenovirus neutralization as measured by VNA and analysis of antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein refer to section 5.8.1.

To assess the changes in the SARS-CoV-2 genome by development of SARS-CoV-2 variants a list of differentially expressed genes will be analyzed using parametric approaches to increase the power of detection. However, the false positive rate may be dramatically increased if the

assumptions of the model distribution are violated. Based on the underlying distribution a method will be chosen and analysis details will be described in the DPS.

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 by presence, severity and duration of COVID-19 signs and symptoms and confirmation of SARS-CoV-2 infection by molecular testing refer to section 5.8.4.

A proportional odds model will be fitted to explore a shift in severity.

Time to resolution of COVID-19 episodes will be described for participants in the Ad26.COV2.S and placebo groups, using the Kaplan-Meier methodology.

For the medical intervention endpoint, a descriptive summary will be provided by type of intervention. A severity adjusted analysis will be done on the medical intervention endpoint (mechanical ventilation and ECMO, ICU, hospitalization).

A frailty index will be calculated at baseline and during the study at certain timepoints. The frailty index will be assessed in participants who received Ad26.COV2.S as compared to placebo.

5.7. (Other) Safety Analyses

Following information will be collected for:

Participants in the Safety Subset:

- Solicited local and systemic adverse events (AEs) for 7 days after vaccination
- Unsolicited AEs for 28 days after vaccination

All participants in the FAS during the entire study:

- Serious adverse events (SAEs) and MAAEs leading to study discontinuation after vaccination

All participants in the FAS during the first 6 months:

- Medically-attended adverse events (MAAEs) after vaccination

Safety analyses will be performed on the FAS. No formal statistical testing of safety data is planned. Safety data by vaccination group will be analyzed descriptively. Specific safety analyses will be performed on the Safety Subset. All safety analyses will be tabulated by treatment group (active vaccine, placebo) according to the as-treated principle. All safety analyses will be presented overall and by age and comorbidity (with/without) strata. The main age strata for reporting purposes are ≥18 to <60 years of age and ≥60 years of age. In addition, safety data will be analyzed by treatment group and participant seropositivity status at screening.

Denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), 95% CI for the mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

Other exploratory or sensitivity analyses may be performed in addition to the analyses described below on an ad-hoc basis.

5.7.1. Adverse Events

5.7.1.1. Definitions

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by participants in their diary. Unsolicited AEs are all AEs for which the participant is not specifically questioned.

Solicited AEs shown in the tables are extracted from the investigator assessment pages (CE) of the CRF (Safety Subset). For unsolicited AEs, only the AEs within the 28-day period following the vaccination will be presented in the safety tables (Safety Subset), except for SAEs and MAAEs leading to study discontinuation, which will be captured and tabulated in the outputs covering the whole study period and for all subjects in the FAS, and MAAEs (including new onset of chronic diseases) which will be captured and tabulated in the outputs covering the 6 month post vaccination period (Phases: Post-dose, Follow-up (D30-M6), and Follow-up (M6-W52)) and for all subjects in the FAS.

Solicited administration site symptoms will be by definition considered as related to the study vaccine.

The severity of the AEs will be classified as grade 1 to 4. Solicited events that are graded less than grade 1, are not considered as AE. In case no grades are available, the grading of the solicited events will occur according to the grading list in Appendix 6.

5.7.1.2. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated with exact 95% CI, when appropriate. Unsolicited AEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (administration site, systemic) and preferred term.

For solicited AEs following tables will be provided: summary, by worst severity grade, at least grade 3, related (systemic only), time to onset (in days) and duration (in days) for most frequent events (>5%) and body temperature. Note: Duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the vaccination period.

For unsolicited AEs following tables will be provided: summary table (including SAE, MAAEs, MAAEs leading to study discontinuation, fatal outcome, and discontinuation), all events, most frequent (>5%), at least grade 3, related and SAE. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

Listings and/or participant narratives will be provided as appropriate, for those participants who die, discontinue study due to an AE, or experience a serious AE.

5.7.1.3. Phase Allocation of Adverse Events

Solicited events are always allocated to the respective Post Dose period.

Step 1: Allocation of events to the periods:

Adverse events in the SDTM data base are allocated to periods based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

- In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.

- In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the trial. In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose 1 period), except if the end date of the AE falls before the start of the first active treatment phase (post dose 1 period).

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same participant with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

If overlapping/consecutive events start in one of the following periods - Screening or post dose extension (i.e. non-active periods) - followed by an AE in - post-dose period (active period) - they are allocated to their respective periods and are considered as separate events.

In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM data base but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

In case overlapping/consecutive events start in both an active period followed by a non-active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM

data base but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.

In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.

Time is not considered when determining overlap of events.

5.7.1.4. Missing Data

Missing data will not be imputed. Participants who do not report an event/concomitant medication will be considered as participants without an event/concomitant medication. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade, but will be considered as not reported for the analysis of at least grade 3.

5.7.2. Vital Signs

No ECG are measured in this study. For HIV Viral Load and CD4 counts only abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the following gradings (absolute CD4+ Count: 300 – 400/mm3 (grade 1); 200 – 299/mm3 (grade 2) 100 – 199/mm3 (grade 3) and < 100/mm3 (grade 4) and for viral load when a subject goes from undetectable to detectable HIV RNA copies/mL.

For all participants, weight and height (and BMI) at baseline will be summarized using descriptive statistics. Vital sign abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the FDA grading table in Appendix 6.

Temperature will be measured at each scheduled time point and summarized using descriptive statistics. A listing of participants with fever will be provided. Other vital signs may be measured at the discretion of the investigator. For those, vital signs abnormalities of at least grade 3 will be listed.

For COVID-19 cases, temperature will be summarized over time from start of symptoms, using descriptive statistics and/or graphically. Temperature and oxygen saturation will be summarized separately for the measures by the participants as well as by the site. For temperature, 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 time point. Descriptive statistics will be calculated for changes between COVID-19 Day 29 and COVID-19 Day 3-5 for vital signs that were captured by the site. The schedule for

COVID-19 cases will start for each participant on Day 1 of a COVID-19 Episode, will be on a daily basis and take the maximum of the values recorded for each subject per day.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emerging. In case a laboratory test result is censored (no numeric value is available, but only a verbatim term) then a numeric value will be imputed by a value exceeding the cut-off value with one unit. (<x: subtract 1 unit from x, >x: add 1 unit to x; <3.45 is imputed with 3.44).

In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades, the following rules are applied:

Worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.

The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a participant has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), results falling in these zones will be allocated to the adjacent worst-case grade (cf Appendix 9 of the CTP).

5.8. Other Analyses

5.8.1. Reactogenicity

For all participants in the safety subset the diary data will be summarized descriptively by treatment group. Temperature will be summarized using the maximum of the recorded temperature per subject by study day, and summarizing incidences of fever using the highest grade of fever observed for each subject using the grading system in Appendix 6. The same approach will be taken for the maximum size of any swelling. All symptoms will be summarized taking the worst grading as captured by the investigator at the Day 28 visit. For all symptoms also incidences of worst gradings will be summarized by Day comparing treatment groups.

5.8.2. Immunogenicity

Blood will be collected from all non-Immuno Subset participants for humoral immunogenicity assessments before vaccination, 28 days after vaccination and at D71, W24 and W52 after vaccination. For a total of approximately 400 participants in the Immuno Subset, blood will be collected for analysis of humoral immune responses before vaccination, 28 days after vaccination, 70 days after vaccination, and 24, 52, 78, and 104 weeks after vaccination.

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 8.

Table 8 Immunogenicity and Transcriptomic Assessments

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
Transcriptomic Assay	**Purpose**
Supportive of Exploratory Objectives	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in unstimulated cells or whole blood

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; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay.

The analysis of immunogenicity will use the PPI set.

For the non-immuno subset, humoral immunogenicity data will be analyzed according to the as-treated principle by vaccine regimen (active vaccine, placebo), by vaccine regimen and participant seropositivity status at screening and by vaccine regimen and COVID-19 (no infection, asymptomatic infection, mild, at least mild, at least moderate, at least severe) and by vaccine regimen and age and comorbidity (with/without) strata, by vaccine regimen and region, by vaccine regimen and emerging CD4 count abnormality (at least grade 1 at any time after vaccination) and viral load (treatment emergent detectable viral load). Specific immunogenicity analyses will be performed on the Immuno Subset. All immunogenicity analyses for the immuno subset will be analyzed by vaccine regimen and by vaccine regimen and age and comorbidity (with/without) strata.

For participants with a COVID-19 episode immunogenicity data will be analyzed by vaccine regimen at baseline, 28 days post vaccination, on COVID-19 Day 3-5 and on COVID-19 Day 29

for the standard immunogenicity assays (S-ELISA and VNA) and on COVID-19 Day 3-5 and on COVID-19 Day 29 for all other assays that are available (Table 6).

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. These analyses will be described in a separate correlates SAP.

5.8.2.1. Parameters

The following humoral immune responses are measured by immunogenicity against the insert using humoral immune responses, including titers of neutralizing antibodies and S-ELISA titers, functional and molecular antibody characterization and RBD antibodies and N-ELISA positivity. Immunogenicity against the vector will be explored using an adenovirus neutralization assay to assess neutralizing antibody responses against the vector.

5.8.2.2. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Values will be imputed based on the type of analysis. For the calculation of the geometric mean titer, values below LLOQ will be imputed to LLOQ/2. While for the calculation of the geometric mean of the increase from baseline, values below LLOQ will be imputed to LLOQ. The LLOQ values per assay are available in the data base.

Data above the ULOQ will be imputed with the ULOQ.

5.8.2.3. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

5.8.2.4. Immunogenicity Against the Insert:

5.8.2.4.1. Humoral assays

For **VNA (**both wild-type virus and pseudovirion expressing S protein, as available) and **S-ELISA** assays following results will be calculated: N, geometric mean[a§]and corresponding 95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented.

For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the log10 transformed values. These values are back transformed to provide the geometric mean and its corresponding 95% CI.

For wild type, pseudovirion VNA and S-ELISA separately:

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[a] calculate the mean and corresponding 95% CI of the $\log^{10}$ transformed values, back-transform this mean [i.e. 10^mean] and CI [i.e. 10^CI].

• A sample will be considered positive if the value is strictly greater than the LLOQ (>LLOQ).

• Responder definition. A post-baseline sample will be considered a responder if at least one of the following conditions is satisfied:

- The baseline sample value is less than or equal to the LLOQ (≤LLOQ) and the post-baseline sample is strictly greater than the LLOQ (>LLOQ)

- The baseline sample value is strictly greater than the LLOQ (>LLOQ) and the post-baseline sample value represents an at least 4-fold (≥4-fold) increase from the baseline sample value.

Actual values are tabulated and shown as box plots with the corresponding geometric mean, 95% CI per time point and minimum and maximum are shown for each assay. For the immuno subset actual values are tabulated and shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay.

In addition, GMT plots over time, combining the regimens in one graph (without individual participant dots) will also be generated.

Participant profiles of the actual values over time will be graphically presented for Covid-19 cases.

Correlation plots between humoral assay results will be provided for selected time points.

In the graphs, original values will be displayed on the $\log^{10}$ scale.

Further details may be provided in the DPS.

For the **N-ELISA** the proportion of participants that are positive will be tabulated.

5.8.2.5. Immunogenicity Against the Vector

For immunogenicity against the Ad26 vector backbone (Adenovirus neutralization by neutralization assay) following statistics will be calculated: geometric mean and corresponding 95% CI of the actual values, and number and percentage of participants with a positive sample.

Correlation plots with the Adeno assays versus the assays against the inserts will be provided for the most important time points.

5.8.3. Definition of Subgroups

Selected safety and efficacy analyses will be summarized by treatment group for the following subgroups:

- sex
- race
- ethnicity

- age categories 1 (18-≤59, ≥60years)
- age categories 2 (18-<40, 40-≤59, ≥60 years)
- age categories 3 (18-<40, 40-≤59, 60-≤69, 70-≤79, ≥80 years)
- region (Africa, North-America, Latin-America, Europe (if applicable), Asia (if applicable)). Regions may be modified/pooled based on participation.
- presence of baseline comorbidity
- seropositivity status (positive vs. negative)
- frailty index

If necessary, for country approval/submission, an analysis by country or country*subgroup interactions may be added.

5.8.4. Patient-Reported Outcomes

5.8.4.1. Symptoms of Infection with Coronavirus-19 (SIC)

The SIC consists of 3 separate parts (symptoms rated from 0 to 10 as part 1, fever as part 2, and 4 separate symptoms as part 3) that are scored separately:

- Part 1: Each symptom is present or absent (0), and if present rated on a 10 point scale from ranging from 0 (None) to 10 (Worst possible).

The **symptom score** is the mean of all scores for each day, during the COVID-19 episode.

The **symptom duration** is the period from the first day of symptoms till the last day with symptoms in Days (calculated as last day with symptoms – first day of symptoms + 1).

The **symptom AUC** is the area under the curve for the complete COVID-19 episode.

The **peak symptom score** is the maximum of all the symptom scores during the COVID-19 episode.

- Part 2: Fever.

Fever will be scored (fever score) as the maximum recorded temperature for each day during the COVID-19 episode.

Fever will be coded as 'Present' if the fever score is ≥38.0 ^{o}C or ≥100.4 ^{o}F and 'Absent' otherwise.

The **total fever days** is the number of days with fever present during the COVID-19 episode.

Fever duration will be the period from the first day with fever till the last day with fever in Days (calculated as last day with fever – first day of fever + 1).

The **peak fever** is the maximum fever score during the COVID-19 episode.

The **fever AUC is** the AUC of fever score during the total of fever days of the COVID-19 episode. (For the AUC if there is a single missing day between days with fever the missing day will be ignored, i.e., interpolation will be used in the calculation of the AUC.)

The fever score will also be coded using FDA grades for fever.

- Part 3: Each of the 4 specific symptoms is either present or absent. The totality of the symptoms is rated on the following scale: 0=None, 1=Mild, 2=Moderate, 3=Severe.

The **specific symptom score** is the mean of all scores during the COVID-19 episode per day.

The **total specific symptom score** is the mean of all scores during the COVID-19 episode.

The **total specific symptom duration** is the duration of specific symptoms during the COVID-19 episode from the first day with a specific symptom till the last day with a specific symptom in Days (calculated as last day with a specific symptom – first day of a specific symptom + 1).

The **total specific reported symptom score** is the mean of all scores during the COVID-19 episode at which a subject has reported at least one specific symptom.

Note 1: For Part 1, total scores will be calculated based on the number of assessments completed by the participant per day and in cases where more than 75% of the items needed to calculate the score is not collected (reported as no answer to the part 1 Yes/No possibility AND no severity rate), then the value for that score will be set to missing. For example, if a participant has responded to 7 or more out of the 25 symptom scale questions the score will be the mean of the available questions. If the participant has only completed 6 or less of the questions then the symptom score will be set to missing, unless a subject has only provided responses 'Yes' to all of the answered questions (then it is assumed that the subject only noted the pertinent symptoms for that day). In case of missing severity rate and the answer was 'yes' the rate will be imputed by '5'.

5.8.4.2. Analysis Methods

SIC scores will be analyzed for participants with any COVID-19 episode based on the PP set.

For continuous variables, number of observations, mean, standard deviation, median, first and third interquartile will be tabulated and means with standard errors will be graphically presented per vaccine regimen and means with standard errors per group and time point (starts since onset of COVID-19 episode). Counts will be tabulated.

These analyses will also be summarized by COVID-19 for each classification (mild, moderate, severe-critical cases) and additionally in a cumulative fashion (at least mild, at least moderate, and all symptomatic cases).

In case a participant experiences two or more episodes, all episodes will be analyzed according to the definitions above. For summaries across treatment groups, the episode classified with the highest severity will be selected. If the worst severity is equal for several episodes, scores of these episodes will be averaged for the participant before calculating overall averages.

5.9. Interim Analyses

Interim analyses are performed in the form of continuous monitoring and are provided in Table 9. No other interim analyses are planned.

Table 9 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 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 receive the vaccine.	one-sided p-value compared to α at 5%, no multiplicity adjustment	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 week, starting from the 20th event after 14 days post dose 1 (Day 15)[b]
Efficacy[c]	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 42nd event 14 days post dose 1 are observed, **then at least weekly thereafter**[c]
Efficacy[c]	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 42nd event 28 days post dose 1 are observed, **then at least weekly thereafter**[c]

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.

[b] Monitoring stops when the primary efficacy analysis is triggered.

[c] The monitoring can only start as soon as the conditions outlined in Section 5.4.1 are met.

All boundaries will be monitored by the Statistical Support Group (SSG). If a boundary has been crossed, then the SSG immediately informs the Chair of the DSMB through secure communication procedures. At this point the DSMB will convene, evaluate the totality of the data and provide a recommendation to the Sponsor.

The study team is responsible for providing the blinded information to the SSG. For relevant definitions regarding a case assignment, see Section 5.2.

5.9.1. Assigning cases for continuous monitoring

Definitions and general case assignment rules are described in Section 5.2.

For continuous monitoring the order of cases will be based on the *onset of symptoms*. An episode of COVID-19 may however start with mild symptoms and may deteriorate to a degree that it satisfies a more severe classification. To avoid situations that an event occurs that already should have been analyzed as based on the onset of symptoms, the approach chosen here is that each case will be analysis-ready at the latest at **Day 15** (see also CTP Section 8.1).

For this approach it is of concern if an event is not resolved at Day 15, AND if that event worsens in severity after analysis-ready status. In the rare case that this happens AND affects one of the 4 monitoring processes, the case will be added to the first upcoming monitoring analysis based on the moment it is established that it satisfies a more severe definition.

Continuous monitoring will be performed on analysis-ready cases known up to that and including that calendar Day; if multiple cases are analysis-ready on a Day, the boundary will be verified for the total number of cases.

For the monitoring of potential severe harm, the event will be entered in the monitoring as soon as the events becomes confirmed as satisfying the severe/critical case definition (from Amendment 5 of the SAP, only severe/critical cases as adjudicated by the Clinical Severity Adjudication Committee will be used in the severe harm monitoring).

The period to define analysis ready- for an episode of COVID-19 to take its course is chosen as it is expected to have limited impact on case classification, and it also allows to assess critical information that is required to determine if the case is part of a continuous monitoring process (and how it should be entered):

- Was the participant included in the FAS? (Note that this means that the participant was randomized and treated.)
- Was the participant treated with the assigned treatment? (Note that if not, the participant would be analyzed *as treated* in the FAS and excluded from the PP population.)
- Was the volume of the injection sufficient (≥80%) according to the drug administration log?
- Was the participant seronegative at baseline?
- Was the participant part of the PP population (see Section 4)?
- Was the onset of symptoms post-vaccination (Day 2 or later)?
- Was the onset of symptoms after Day 14 (Day 15 or later) or Day 28 (Day 29 or later)?

5.9.2. Harm monitoring for excess symptomatic COVID-19 cases

Continuous monitoring for vaccine-associated *enhanced* COVID-19 will be performed based on *symptomatic* COVID-19 events in the FAS population. Only cases where the onset of symptoms is on Day 2 or later will be included. Monitoring for harm will be performed on a daily basis on analysis-ready cases only.

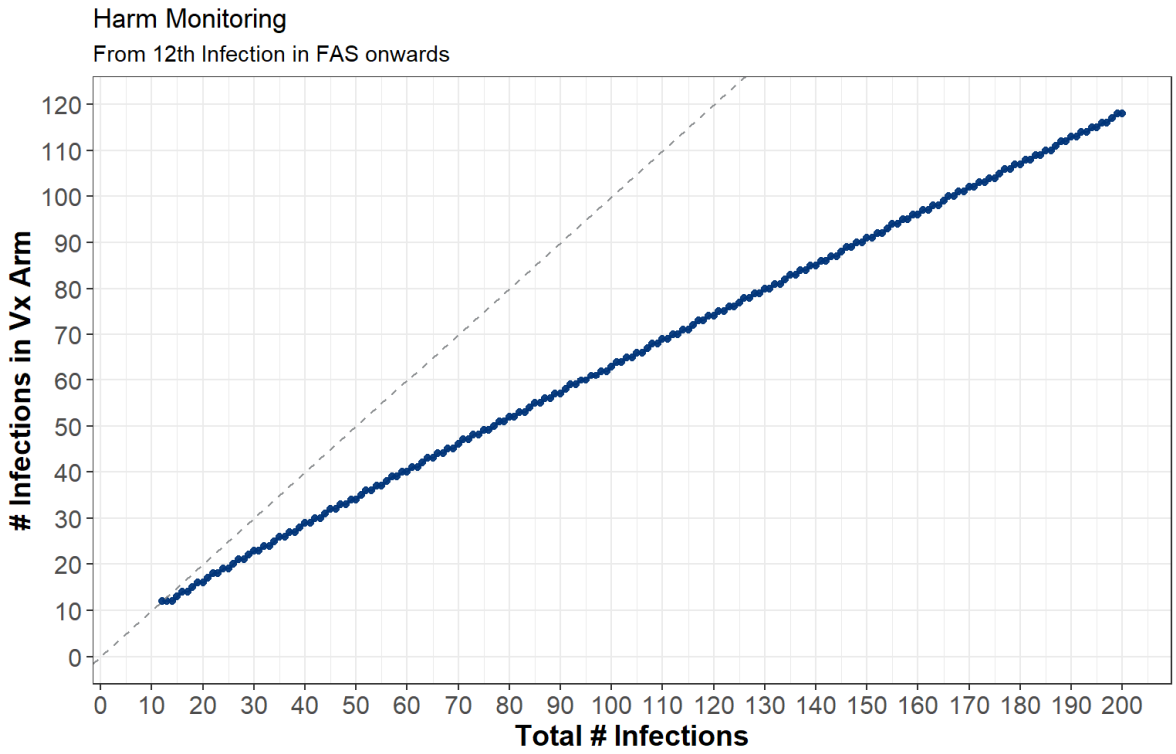
The monitoring starts when there are in total 12 analysis-ready symptomatic cases observed and will continue to be monitored on each calendar day until the primary analysis is triggered. In order to calculate the boundaries for this monitoring while controlling overall alpha level as specified (i.e. 5% overall alpha) an assumption must be made on maximum number of looks that will have to be made. For this purpose, it is assumed that there will be a maximum of 200 symptomatic cases

in the FAS before the primary analysis is triggered. This leads to the following boundaries on the number of events in the placebo treatment group for each total number of events. Starting at 12 analysis-ready cases, the boundary is crossed if there are 0 or 1 analysis-ready cases on placebo and all other cases are on active treatment. If there are 2 analysis-ready cases on placebo, the boundary is crossed if the total is 14 cases (i.e., 12 on active), etcetera (Table 10). The boundary is illustrated graphically in Figure 4.

Table 10 The number of Symptomatic Cases on Placebo and Total number of Symptomatic Cases at which Point the Boundary is Crossed (FAS)

Placebo	Total	Placebo	Total	Placebo	Total	Placebo	Total
≤1	12	22	65	43	113	64	160
2	14	23	67	44	115	65	162
3	17	24	69	45	118	66	164
4	20	25	72	46	120	67	167
5	23	26	74	47	122	68	169
6	25	27	76	48	124	69	171
7	28	28	79	49	127	70	173
8	31	29	81	50	129	71	175
9	33	30	83	51	131	72	178
10	36	31	86	52	133	73	180
11	38	32	88	53	136	74	182
12	41	33	90	54	138	75	184
13	43	34	93	55	140	76	186
14	46	35	95	56	142	77	189
15	48	36	97	57	144	78	191
16	50	37	99	58	147	79	193
17	53	38	102	59	149	80	195
18	55	39	104	60	151	81	197
19	58	40	106	61	153	82	200
20	60	41	109	62	156		
21	62	42	111	63	158		

Figure 4 Harm Monitoring Boundary - Active versus Total Number of Symptomatic Cases (FAS)



5.9.3. Harm monitoring for excess severe COVID-19 cases

Vaccine harm monitoring is intended to monitor for vaccine-induced enhanced disease and will be performed for severe/critical COVID-19 cases based on the FAS each calendar day. Specifically, monitoring for a higher rate of severe/critical disease or death starts at the 5th event, until the harm boundary is reached, or until the primary efficacy analysis is triggered. Monitoring for harm of severe/critical COVID-19 cases will be performed on a daily basis on all available severe cases, irrespective of their analysis ready status. (from Amendment 5 of the SAP, only severe/critical cases as adjudicated by the Clinical Severity Adjudication Committee will be used in the severe harm monitoring).

The monitoring excess severe is done using an exact one-sided binomial test of the null hypothesis $H_0: p \leq 1/2$ versus the alternative hypothesis $H_1: p > 1/2$, where p is the probability that an -infected participant was assigned to the vaccine arm (as opposed to being assigned to the placebo arm). The testing for harm starts at the 5th total severe cases in the FAS and is performed continuously through the primary analysis. Each test is performed at an uncorrected one-sided significance level of $\alpha = 0.05$.

5.9.4. Non-efficacy monitoring

The non-efficacy monitoring is based on analysis-ready moderate/severe cases in the FAS, where a participant must be seronegative at baseline to be included in this boundary monitoring. Every effort will be made to establish seronegativity in time. In the unlikely case seronegativity is not

established in time for a case that is to be included in a monitoring calculation otherwise (ie, on Day 14 of an episode), the case will only be included for non-efficacy monitoring at the time seronegativity is established; monitoring calculations will not be repeated at that time.

This boundary will be verified starting once 20 analysis-ready moderate/severe cases in the FAS (seropositive) are observed. From that point onwards, after at least weekly, the boundary will be checked on analysis-ready cases. Monitoring for non-efficacy stops when the primary analysis is triggered. The boundary to be used for non-efficacy is provided in Table 11 and illustrated in Figure 5 , and is based on the case splits that trigger the rules as defined in Table 9 using the methods laid out in Appendix 8 with the exact binomial based confidence intervals.

Table 11 The Number of Confirmed Moderate/Severe Cases on Placebo and Total Number of Confirmed Moderate/Severe Cases at which Point the Non-efficacy Boundary has been Crossed (FAS – seronegative)

Placebo	Total	Placebo	Total	Placebo	Total	Placebo	Total
≤7	20	27	56	47	91	67	126
8	21	28	58	48	93	68	127
9	23	29	60	49	95	69	129
10	25	30	61	50	96	70	131
11	27	31	63	51	98	71	132
12	29	32	65	52	100	72	134
13	31	33	67	53	102	73	136
14	32	34	68	54	103	74	138
15	34	35	70	55	105	75	139
16	36	36	72	56	107	76	141
17	38	37	74	57	108	77	143
18	40	38	75	58	110	78	144
19	42	39	77	59	112	79	146
20	43	40	79	60	114	80	148
21	45	41	81	61	115	81	150
22	47	42	82	62	117	82	151
23	49	43	84	63	119	83	153
24	51	44	86	64	120	84	155
25	52	45	88	65	122	85	156
26	54	46	89	66	124	86	158

Figure 5 Boundary for Non-Efficacy (FAS, seronegative)

5.9.5. Efficacy monitoring

As the efficacy monitoring is linked to the co-primary endpoints, the statistical details on efficacy monitoring are already described in the corresponding section, section 5.4.

Table 12 describes the number of analysis-ready co-primary endpoints required as a fraction of the total number of cases in order to stop and reject the primary study hypotheses, and is illustrated in Figure 6.

If the prespecified boundary is met for both co-primary endpoints in the situation that the constraints have also been met (a minimum of 42 molecularly confirmed, moderate to severe/critical COVID-19 cases including 6 in the population of participants aged 60 years or older with onset at least 28 days after vaccination, a minimum of 5 of molecularly confirmed severe/critical COVID-19 cases in the placebo group with onset at least 28 days after vaccination with a favorable split for both co-primary endpoints), the SSG will inform the DSMB and, if deemed appropriate by the DSMB, a meeting with the DSMB 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

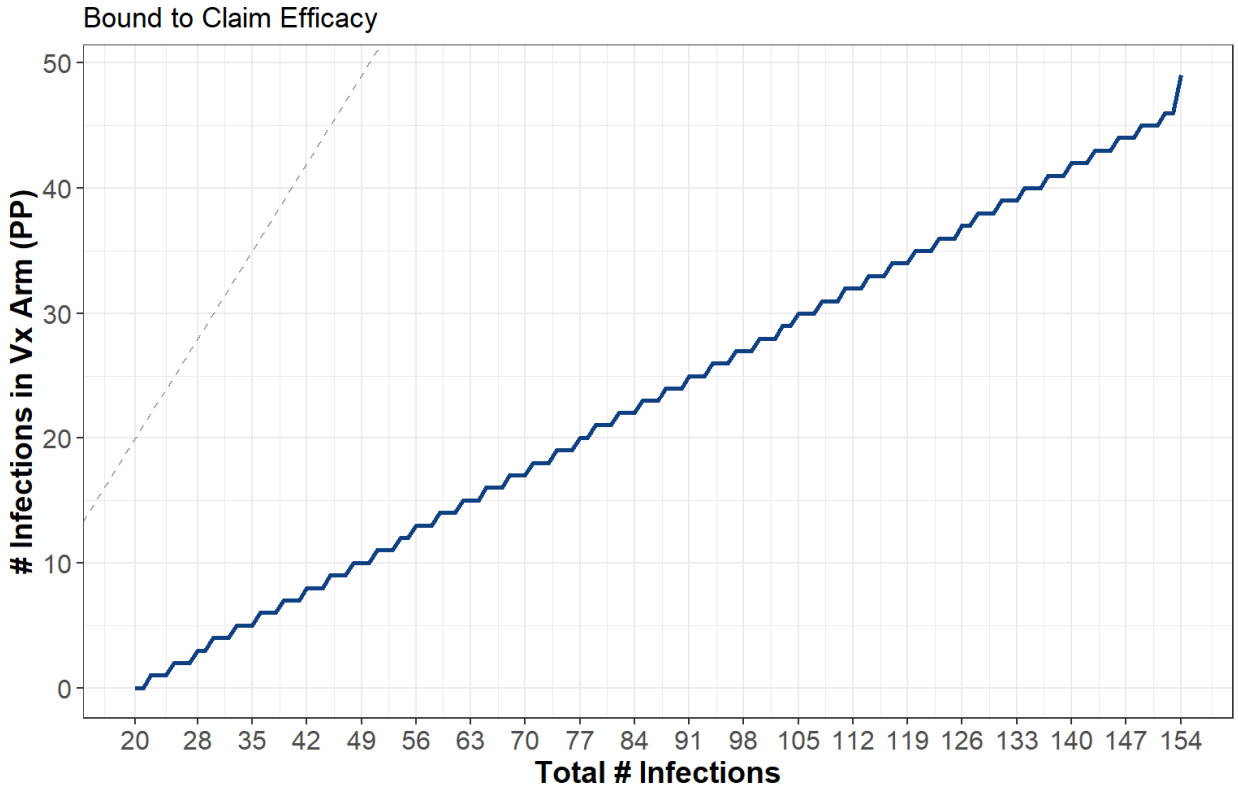
transmitted securely to the appropriate regulatory agency. The sponsor will remain blinded until the data base for the primary analysis is locked or until the time of the snapshot analysis.

Table 12 The Number of Confirmed Moderate/severe Cases on Active and Total Number of Confirmed Moderate/severe Cases at which Point the Efficacy Boundary has been Crossed (PP)

Active	Total	Active	Total	Active	Total
0	20	16	65	32	111
1	22	17	68	33	114
2	25	18	71	34	117
3	28	19	74	35	120
4	30	20	77	36	123
5	33	21	79	37	126
6	36	22	82	38	128
7	39	23	85	39	131
8	42	24	88	40	134
9	45	25	91	41	137
10	48	26	94	42	140
11	51	27	97	43	143
12	54	28	100	44	146
13	56	29	103	45	149
14	59	30	105	46	152
15	62	31	108	49	154

The blinded total number of infections in the FAS with onset of infection after study vaccination may be monitored to track progress and ensure timely cleaning to facilitate operationalization of data base lock.

Figure 6 Boundary for Efficacy (PP)



5.9.6. Sample size monitoring

The incidence of moderate to severe COVID-19 seen in the US and reported in other COVID-19 vaccine trials is significantly higher than assumed at the time of protocol planning. Furthermore, based on that incidence and modeling there is a high degree of probability that a signal of efficacy meeting the prespecified criteria in the protocol amendment 3 will be reached at or prior to the time when 50% of participants will have been followed for 8 weeks from the time of immunization, therefore the sample size was reduced from 60,000 to approximately 40,000.

5.9.7. Data and Safety Monitoring Board (DSMB)

The study will be formally monitored by a DSMB (also known as an Independent Data Monitoring Committee or IDMC). In general, the DSMB will monitor safety data on a regular basis to ensure the continuing safety of the participants. Enrollment (if applicable) will not be paused during regular safety reviews. The DSMB will review unblinded data. The DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter and DSMB Charter Addendum.

The DSMB will also review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b is initiated, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

Continuous monitoring of safety and (non-) efficacy is described in detail in Section 5. If a boundary is met, the SSG immediately informs the DSMB through secure communication procedures. At this point a quorum of the DSMB will be convened as soon as possible and provide a recommendation to the Oversight Group. See also Section 9.8 of the CTP.

5.9.8. Clinical Severity Adjudication Committee

In addition to independently assessing all potential severe/critical COVID-19 cases that meet the severe/critical definition as described in Section 5.2.2.3, a blinded Clinical Severity Adjudication Committee will be established to evaluate a subset of cases of molecularly confirmed moderate to severe/critical COVID-19, for severity as part of the primary and secondary endpoints, as defined in Section 1.1. This committee will consist of independent clinical infectious disease experts and pulmonologists. The committee's deliberations and conclusions will be documented and will be provided to the sponsor. Classification of a case as severe/critical by the Clinical Severity Adjudication Committee is considered definitive.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ATC	anatomic and therapeutic class
BMI	body mass index
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CI	confidence interval
CRF	case report form
CTP	clinical trial protocol
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FAS	full analysis set
FDA	Food and Drug Administration
GMC	geometric mean antibody concentration
GMT	geometric mean titer
GSD	group sequential design
HR	hazard ratio
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IFNg	interferon gamma
IL2	interleukin 2
IRR	incidence rate ratio
ITT	intent-to-treat
LLOQ	lower limit of quantification
NA	not applicable
PBMC	peripheral blood mononuclear cells
PP	per protocol efficacy analysis set
PPI	per protocol immunogenicity analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SFU	spot forming units
SN	seronegative
SP	seropositive
TNE	target number of events
SPRT	sequential probability ratio test
TNFa	tumor necrosis factor alpha
ULOQ	upper limit of quantification
VE	vaccine efficacy
VNA	virus neutralizing antibody
vp	virus particle
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

SAP according to EDMS-RIM-50860, Amendment 3

History:

SAP Version	**CTP Version**
1	Initial release
2	SAP according to EDMS-RIM-50860, Amendment 1
3	SAP according to EDMS-RIM-50860, Amendment 2
4	SAP according to EDMS-RIM-50860, Amendment 3

6.3. Appendix 3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Table 13 presents a list of the demographic variables that will be summarized by vaccine regimen and overall for the FAS. Demographics will also be summarized by region using the FAS.

Table 13 Demographic Variables

Continuous Variables:	Summary Type
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age categories 1 (18-≤59, ≥60 years)	Frequency distribution with the number and percentage of participants in each category.
Age categories 2 (18-<40, 40-≤59, ≥60 years)	
Age categories 3 (18-<40, 40-≤59, 60-≤69, 70-≤79, ≥80 years)	
Sex (male, female, unknown, intersex)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2])	
Working Status	
Profession	
Breastfeeding (yes, no)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.4. Appendix 4 Protocol Deviations

Major protocol deviations and major protocol deviations potentially impacting immunogenicity or efficacy (see section 4) will be summarized.

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to data base lock and the participants with major protocol deviations will be summarized by category.

[Developed withdrawal criteria but not withdrawn]

[Entered but did not satisfy criteria]

[Received a disallowed concomitant treatment]

[Received wrong treatment or incorrect dose]

[Other]

6.5. Appendix 5 Prior and Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

For all participants, concomitant therapies associated with an SAE will be collected and recorded in the eCRF from the moment of vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study. The proportion of participants with concomitant medication associated with these SAEs and MAAEs will be tabulated with exact 95% CI.

For all participants, concomitant therapies associated with COVID-19 will be captured in the electronic eCRF for the duration of the study. The proportion of participants with new concomitant medication associated with these cases will be tabulated with exact 95% CI. New concomitant medications are defined as medications not available at baseline or medication with an increased dosage (See below, New Concomitant Medications, for details), compared to baseline. Baseline medications are all medications reported prior to and at the day of vaccination. In case a baseline medication is reported multiple times then only the last available record reported prior to or at the day of vaccination will be used.

For participants in the Safety Subset, concomitant therapies associated with unsolicited AEs will be collected, recorded in the eCRF from the time of vaccination through 28 days after vaccination and the proportion of participants with concomitant medication will be tabulated with exact 95% CI. Concomitant therapies associated with solicited AEs will be collected by the participants, recorded in the eCRF from the time of vaccination through 7 days after vaccination and the proportion of participants with concomitant medication will be tabulated with exact 95% CI.

Based on their start and stop date, concomitant therapies will be reported in each applicable phase.

If a concomitant therapy record misses components of its start and/or stop dates (time, day and/or month and/or year):

In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods. In case it is clear the medication was taken after vaccination, the start will be allocated to the correct phase without the use of the start dates (time, day and/or month and/or year). In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

There will be special attention to any systemic use of analgesics/antipyretics, started during 8 days following each vaccination (00:00 of day of vaccination + 7 days). Following CMCLASCD (ATC/DD codes) will be used for this: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC

PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION). The classes will be added in a footnote in all related tables and listings. For the use of analgesics/antipyretics which are taken on the day of vaccination an exception is made in case the time is before vaccination. In this case the concomitant medication is also allocated to the post-dose period.

New Concomitant Medications – Increase in dosage Calculation

In case a participant receives the same medication with the same form at baseline and during an COVID-19 episode, then in order to identify whether there was an increase in dose between baseline and the episode the medication dose will be calculated by multiplying the dosage per administration with the number of administrations per day or per week, as applicable for both timepoints and compared.

This rule applies for the following medication frequencies:

- Once weekly (1 time per week)
- Twice weekly (2 times per week)
- Three Times weekly (3 times per week)
- Four Times weekly (4 times per week)
- Twice Daily (BID)
- Twice per Month (BIM)
- Every two weeks (Every 2 weeks)
- Every four weeks (Every 4 weeks)
- Weekly (Every week)
- Once
- Per Year
- Every three months (Q3M)
- Daily (QD)
- Four times daily (Q1D)
- Monthly (QM)
- Every Other Day (QOD)
- Three times daily (TID)

For frequencies equal to ‘other’at baseline, any change to one of the above frequencies will beconsidered an increase, given that the form remains the same. For frequencies equal to ‘as necessary’ (PNR) or ‘occasional’, any change to another frequency or dose will be considered as an increase. A change from ‘as necessary’ (PNR) to ‘occasional’ or ‘other’ will not be considered as an increase.

Moreover, capsule and tablet are considered the same form so to define if there was an increase the dose and the frequency will be used as defined above. The same applies for inhalant and aerosol.

6.6. Appendix 6 FDA Toxicity Grading Scale for Vaccine Trials

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.

6.7. Appendix 7 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. * Smoking and controlled grade 1 hypertension are allowed per protocol and are not exclusion criteria.

6.8. Appendix 8 Statistical Methodology for Poisson Regression

Vaccine efficacy is defined as 1 minus the ratio of the expected incidence rate of cases of COVID-19 in the active group compared to the expected incidence rate in the placebo group.

Vaccine efficacy can be estimated by:

$$\widehat{VE} = 1 - \frac{n_2/N_2}{n_1/N_1} = 1 - \frac{r * n_2}{n_1}$$

Where:

n_2 = number of cases in the vaccinated group
N_2 = follow-up time in the vaccinated group
n_1 = number of cases in the control group
N_1 = follow-up time in the control group
r = $\frac{N_1}{N_2}$.

Let $n = n_1 + n_2$ denote the total number of cases. Suppose that $n_i|N_1, N_2 \sim Poisson(N_i p_i)$, $i = 1,2$, so that $VE = 1 - p_2/p_1$. In this case, conditionally on n and r, n_2 is binomially distributed as $B(n, \pi)$, where $\pi = N_2 p_2/(N_1 p_1 + N_2 p_2) = (1 - VE)/(r + 1 - VE)$.

Let $q = n_2/n$ denote the proportion of cases in the vaccine group. Then, the vaccine efficacy estimator can be rewritten as:

$$\widehat{VE} = 1 - \frac{n_2}{n} * \frac{r * n}{(n - n_2)} = 1 - \frac{r * q}{(1 - q)}$$

Therefore, there is a monotonically decreasing link between the estimated VE and $q = n_2/n$, the observed proportion of cases in the vaccine group among the total cases, and so rejecting a hypothesis for extreme values of q is equivalent to rejecting that same hypothesis for inversely extreme values of $\widehat{VE}$.

Given the sequential testing strategy, the confidence interval for the vaccine efficacy will be adjusted accounting for repeated testing. At the primary analysis when the boundary is crossed or at 154 events, the vaccine efficacy estimate will be reported using the estimated VE (as detailed above) at the time of analysis, accompanied with $(1 - 2\alpha^*)\%$ two sided CI, where alpha* is the type I error at that time. Using the exact binomial CI for p an (adjusted) exact Poisson regression CI can be constructed (Dragalin et al, 2002; Nauta, 2011). In section X1 the R code to generate the SPRT bounds and to derive the relevant $(1 - 2\alpha^*)\%$ levels is given. The results of the code are presented in Table 14.

1. Section X1: R code SPRT

```
# Code to generate the curtailed SPRT boundaries
# required libraries: gsDesign -- version 3.1.1
# setting the parameters
V0 <- 0.3
V1 <- 0.60
a <- 0.025
b <- 0.1
h <- 1
pi1 <- (1 - V1) / (1 + h - V1)
pi0 <- (1 - V0) / (1 + h - V0)
# Single-stage UMP binomial test
UMP <- gsDesign::nBinomial1Sample(p0 = pi1, p1 = pi0, alpha = b, beta = a, n = 10:200,
outtype = 2)
UMP
# Setup of the curtailed SPRT bounds
# need 154 events
maxn <- UMP$n
# and have for 1-stage test upper bound of 52
upper <- UMP$b
# start the SPRT at 20 events
minn <- 20
# set the last test so that alpha remains under 0.025; higher values of upper
# will result in inflation, lower values in loss of power
cb <- upper - 3
# generate the bounds from minn to maxn
x <- gsDesign::binomialSPRT(p0 = pi1, p1 = pi0, alpha = b, beta = a, minn = minn, maxn
= maxn)
Vx_bounds <- x$lower$bound
k <- length(Vx_bounds)
# set the bound of the last test at cb
Vx_bounds[k] <- cb
# no testing for futility
bb <- rep(maxn+1, length = k)
# assess the operating characteristics under pi1 and pi0
y <- gsDesign::gsBinomialExact(k = k, theta = c(pi1, pi0), n.I = minn:(minn + k - 1),
a = Vx_bounds, b = bb)
# power and type I
colSums(y$lower$prob)
# output object
out <- data.frame(Total_Infections = y$n.I,
       Vx_Arm = Vx_bounds,
       Obs_VE = 1-(Vx_bounds/y$n.I)/((y$n.I-Vx_bounds)/y$n.I),
       Cum_alpha = cumsum(y$lower$prob[,2]),
       alpha_per_test=y$lower$prob[,2],
       Nominal_alpha = pbinom(Vx_bounds, y$n.I, prob=pi0),
       Power_VE_60= cumsum(y$lower$prob[,1]))
out
```

Table 14 Results of the SPRT code

	Total Infections	Vx Arm	Observed VE	Cumulative α	α per test	Nominal α	Power (VE 60%)
Analysis 1	20	0	1.000000	0.000025	0.000025	0.000025	0.001195
Analysis 2	21	0	1.000000	0.000025	0.000000	0.000014	0.001195
Analysis 3	22	1	0.952381	0.000144	0.000119	0.000140	0.006074
Analysis 4	23	1	0.954545	0.000144	0.000000	0.000086	0.006074
Analysis 5	24	1	0.956522	0.000144	0.000000	0.000052	0.006074
Analysis 6	25	2	0.913043	0.000339	0.000195	0.000287	0.014252
Analysis 7	26	2	0.916667	0.000339	0.000000	0.000182	0.014252
Analysis 8	27	2	0.920000	0.000339	0.000000	0.000115	0.014252
Analysis 9	28	3	0.880000	0.000609	0.000270	0.000469	0.025810
Analysis 10	29	3	0.884615	0.000609	0.000000	0.000306	0.025810
Analysis 11	30	4	0.846154	0.001175	0.000566	0.001002	0.046241
Analysis 12	31	4	0.851852	0.001175	0.000000	0.000671	0.046241
Analysis 13	32	4	0.857143	0.001175	0.000000	0.000448	0.046241
Analysis 14	33	5	0.821429	0.001744	0.000569	0.001289	0.067262
Analysis 15	34	5	0.827586	0.001744	0.000000	0.000880	0.067262
Analysis 16	35	5	0.833333	0.001744	0.000000	0.000599	0.067262
Analysis 17	36	6	0.800000	0.002339	0.000595	0.001565	0.089746
Analysis 18	37	6	0.806452	0.002339	0.000000	0.001088	0.089746
Analysis 19	38	6	0.812500	0.002339	0.000000	0.000753	0.089746
Analysis 20	39	7	0.781250	0.002951	0.000612	0.001822	0.113398
Analysis 21	40	7	0.787879	0.002951	0.000000	0.001285	0.113398
Analysis 22	41	7	0.794118	0.002951	0.000000	0.000903	0.113398
Analysis 23	42	8	0.764706	0.003569	0.000618	0.002057	0.137842
Analysis 24	43	8	0.771429	0.003569	0.000000	0.001470	0.137842
Analysis 25	44	8	0.777778	0.003569	0.000000	0.001045	0.137842
Analysis 26	45	9	0.750000	0.004184	0.000615	0.002265	0.162739
Analysis 27	46	9	0.756757	0.004184	0.000000	0.001637	0.162739
Analysis 28	47	9	0.763158	0.004184	0.000000	0.001178	0.162739
Analysis 29	48	10	0.736842	0.004790	0.000605	0.002448	0.187805
Analysis 30	49	10	0.743590	0.004790	0.000000	0.001787	0.187805
Analysis 31	50	10	0.750000	0.004790	0.000000	0.001299	0.187805
Analysis 32	51	11	0.725000	0.005380	0.000590	0.002604	0.212815
Analysis 33	52	11	0.731707	0.005380	0.000000	0.001919	0.212815
Analysis 34	53	11	0.738095	0.005380	0.000000	0.001408	0.212815
Analysis 35	54	12	0.714286	0.005952	0.000572	0.002736	0.237591
Analysis 36	55	12	0.720930	0.005952	0.000000	0.002033	0.237591
Analysis 37	56	13	0.697674	0.006887	0.000936	0.003782	0.271760
Analysis 38	57	13	0.704545	0.006887	0.000000	0.002844	0.271760
Analysis 39	58	13	0.711111	0.006887	0.000000	0.002129	0.271760
Analysis 40	59	14	0.688889	0.007651	0.000764	0.003871	0.300287
Analysis 41	60	14	0.695652	0.007651	0.000000	0.002931	0.300287

Analysis 42	61	14	0.702128	0.007651	0.000000	0.002209	0.300287
Analysis 43	62	15	0.680851	0.008342	0.000691	0.003935	0.326691
Analysis 44	63	15	0.687500	0.008342	0.000000	0.002998	0.326691
Analysis 45	64	15	0.693878	0.008342	0.000000	0.002274	0.326691
Analysis 46	65	16	0.673469	0.008980	0.000638	0.003977	0.351653
Analysis 47	66	16	0.680000	0.008980	0.000000	0.003047	0.351653
Analysis 48	67	16	0.686275	0.008980	0.000000	0.002325	0.351653
Analysis 49	68	17	0.666667	0.009574	0.000594	0.003999	0.375428
Analysis 50	69	17	0.673077	0.009574	0.000000	0.003080	0.375428
Analysis 51	70	17	0.679245	0.009574	0.000000	0.002362	0.375428
Analysis 52	71	18	0.660377	0.010129	0.000555	0.004004	0.398148
Analysis 53	72	18	0.666667	0.010129	0.000000	0.003098	0.398148
Analysis 54	73	18	0.672727	0.010129	0.000000	0.002388	0.398148
Analysis 55	74	19	0.654545	0.010649	0.000519	0.003993	0.419895
Analysis 56	75	19	0.660714	0.010649	0.000000	0.003104	0.419895
Analysis 57	76	19	0.666667	0.010649	0.000000	0.002403	0.419895
Analysis 58	77	20	0.649123	0.011135	0.000486	0.003969	0.440729
Analysis 59	78	20	0.655172	0.011135	0.000000	0.003098	0.440729
Analysis 60	79	21	0.637931	0.011909	0.000774	0.005002	0.468684
Analysis 61	80	21	0.644068	0.011909	0.000000	0.003934	0.468684
Analysis 62	81	21	0.650000	0.011909	0.000000	0.003083	0.468684
Analysis 63	82	22	0.633333	0.012524	0.000615	0.004927	0.491412
Analysis 64	83	22	0.639344	0.012524	0.000000	0.003889	0.491412
Analysis 65	84	22	0.645161	0.012524	0.000000	0.003058	0.491412
Analysis 66	85	23	0.629032	0.013070	0.000545	0.004843	0.512020
Analysis 67	86	23	0.634921	0.013070	0.000000	0.003835	0.512020
Analysis 68	87	23	0.640625	0.013070	0.000000	0.003027	0.512020
Analysis 69	88	24	0.625000	0.013565	0.000496	0.004751	0.531182
Analysis 70	89	24	0.630769	0.013565	0.000000	0.003775	0.531182
Analysis 71	90	24	0.636364	0.013565	0.000000	0.002988	0.531182
Analysis 72	91	25	0.621212	0.014020	0.000455	0.004654	0.549186
Analysis 73	92	25	0.626866	0.014020	0.000000	0.003708	0.549186
Analysis 74	93	25	0.632353	0.014020	0.000000	0.002945	0.549186
Analysis 75	94	26	0.617647	0.014441	0.000420	0.004552	0.566200
Analysis 76	95	26	0.623188	0.014441	0.000000	0.003637	0.566200
Analysis 77	96	26	0.628571	0.014441	0.000000	0.002896	0.566200
Analysis 78	97	27	0.614286	0.014830	0.000390	0.004445	0.582333
Analysis 79	98	27	0.619718	0.014830	0.000000	0.003561	0.582333
Analysis 80	99	27	0.625000	0.014830	0.000000	0.002844	0.582333
Analysis 81	100	28	0.611111	0.015192	0.000362	0.004337	0.597669
Analysis 82	101	28	0.616438	0.015192	0.000000	0.003483	0.597669
Analysis 83	102	28	0.621622	0.015192	0.000000	0.002788	0.597669
Analysis 84	103	29	0.608108	0.015529	0.000337	0.004225	0.612271

Analysis 85	104	29	0.613333	0.015529	0.000000	0.003401	0.612271
Analysis 86	105	30	0.600000	0.016063	0.000534	0.005082	0.631765
Analysis 87	106	30	0.605263	0.016063	0.000000	0.004113	0.631765
Analysis 88	107	30	0.610390	0.016063	0.000000	0.003318	0.631765
Analysis 89	108	31	0.597403	0.016485	0.000422	0.004932	0.647532
Analysis 90	109	31	0.602564	0.016485	0.000000	0.004000	0.647532
Analysis 91	110	31	0.607595	0.016485	0.000000	0.003234	0.647532
Analysis 92	111	32	0.594937	0.016857	0.000372	0.004783	0.661771
Analysis 93	112	32	0.600000	0.016857	0.000000	0.003887	0.661771
Analysis 94	113	32	0.604938	0.016857	0.000000	0.003149	0.661771
Analysis 95	114	33	0.592593	0.017195	0.000337	0.004635	0.674967
Analysis 96	115	33	0.597561	0.017195	0.000000	0.003774	0.674967
Analysis 97	116	33	0.602410	0.017195	0.000000	0.003063	0.674967
Analysis 98	117	34	0.590361	0.017504	0.000309	0.004490	0.687334
Analysis 99	118	34	0.595238	0.017504	0.000000	0.003662	0.687334
Analysis 100	119	34	0.600000	0.017504	0.000000	0.002978	0.687334
Analysis 101	120	35	0.588235	0.017789	0.000285	0.004346	0.698997
Analysis 102	121	35	0.593023	0.017789	0.000000	0.003550	0.698997
Analysis 103	122	35	0.597701	0.017789	0.000000	0.002892	0.698997
Analysis 104	123	36	0.586207	0.018052	0.000264	0.004204	0.710038
Analysis 105	124	36	0.590909	0.018052	0.000000	0.003440	0.710038
Analysis 106	125	36	0.595506	0.018052	0.000000	0.002807	0.710038
Analysis 107	126	37	0.584270	0.018297	0.000245	0.004066	0.720520
Analysis 108	127	37	0.588889	0.018297	0.000000	0.003332	0.720520
Analysis 109	128	38	0.577778	0.018684	0.000387	0.004774	0.734481
Analysis 110	129	38	0.582418	0.018684	0.000000	0.003930	0.734481
Analysis 111	130	38	0.586957	0.018684	0.000000	0.003225	0.734481
Analysis 112	131	39	0.576087	0.018989	0.000305	0.004606	0.745749
Analysis 113	132	39	0.580645	0.018989	0.000000	0.003797	0.745749
Analysis 114	133	39	0.585106	0.018989	0.000000	0.003121	0.745749
Analysis 115	134	40	0.574468	0.019257	0.000269	0.004443	0.755911
Analysis 116	135	40	0.578947	0.019257	0.000000	0.003667	0.755911
Analysis 117	136	40	0.583333	0.019257	0.000000	0.003018	0.755911
Analysis 118	137	41	0.572917	0.019501	0.000243	0.004284	0.765319
Analysis 119	138	41	0.577320	0.019501	0.000000	0.003540	0.765319
Analysis 120	139	41	0.581633	0.019501	0.000000	0.002918	0.765319
Analysis 121	140	42	0.571429	0.019723	0.000223	0.004129	0.774129
Analysis 122	141	42	0.575758	0.019723	0.000000	0.003416	0.774129
Analysis 123	142	42	0.580000	0.019723	0.000000	0.002819	0.774129
Analysis 124	143	43	0.570000	0.019928	0.000205	0.003979	0.782433
Analysis 125	144	43	0.574257	0.019928	0.000000	0.003296	0.782433
Analysis 126	145	43	0.578431	0.019928	0.000000	0.002723	0.782433
Analysis 127	146	44	0.568627	0.020118	0.000190	0.003834	0.790292

Analysis 128	147	44	0.572816	0.020118	0.000000	0.003179	0.790292
Analysis 129	148	44	0.576923	0.020118	0.000000	0.002630	0.790292
Analysis 130	149	45	0.567308	0.020294	0.000176	0.003693	0.797753
Analysis 131	150	45	0.571429	0.020294	0.000000	0.003066	0.797753
Analysis 132	151	45	0.575472	0.020294	0.000000	0.002539	0.797753
Analysis 133	152	46	0.566038	0.020458	0.000164	0.003556	0.804851
Analysis 134	153	46	0.570093	0.020458	0.000000	0.002956	0.804851
Analysis 135	154	49	0.533333	0.023976	0.003518	0.010603	0.862198

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