Protocol

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

Protocol for: Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med. DOI: 10.1056/NEJMoa2034201

Interim results of a Phase 1/2a trial with the Ad26.COV2.S Covid-19 Vaccine

This supplement contains the following items:

1. Original protocol, final protocol including a summary of changes.
2. Original statistical analysis plan, no changes applied

Janssen Vaccines & Prevention B.V.*

Clinical Protocol

Protocol Title

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26COVS1 in Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older

Protocol VAC31518COV1001; Phase 1/2a

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(s):

IND: PS005513 (pre-assignment)
EudraCT NUMBER: 2020-001483-28

Status: Approved for Dossier Use
Date: 20 April 2020
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-ERI-207834851

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

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26COVS1 in Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older

Ad26COVS1 is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus spike (S) protein, which will be assessed in this study. This will be the first-in-human (FIH) study for Ad26COVS1.

OBJECTIVES AND ENDPOINTS

A description of study cohorts is provided in the Overall Design section below.

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26COVS1 at 2 dose levels, 5×10^{10} vp and 1×10^{11} vp, administered intramuscularly (IM) as a single-dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	All participants in Cohorts 1, 2, and 3: • Solicited local and systemic adverse events (AEs) for 7 days after each vaccination • Unsolicited AEs for 28 days after each vaccination • Serious adverse events (SAEs) throughout the study (from first vaccination until end of the study; SAEs occurring before the first vaccination will be summarized separately).

Objectives	Endpoints
Secondary	
• To assess the humoral and cellular immune response to Ad26COVS1	Humoral Immune Response All participants in Cohorts 1, 2, and 3: • SARS-CoV-2 neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay (VNA [wild-type virus and/or pseudovirion expressing S protein]) • SARS-CoV-2-binding antibodies measured by enzyme-linked immunosorbent assay (ELISA): Analysis of antibodies binding to the SARS-CoV-2 S protein. Cellular Immune Response A subset of participants in Cohorts 1, 2, and 3: • Th1 and Th2 immune responses as assessed by: o Flow cytometry after SARS-CoV-2 S protein peptide stimulation of peripheral blood mononuclear cells (PBMC) and intracellular staining [ICS] including CD4+/CD8+, interferon gamma [IFNγ], interleukin [IL]-2, tumor necrosis factor alpha [TNFα], IL-4, IL-5, IL-13, and/or other Th1/Th2 markers. Or o Dual or single IFNγ and IL-4 enzyme-linked immunospot (ELISpot) assay after stimulation of PBMC with SARS-CoV-2 S protein peptides.

Objectives	Endpoints
Exploratory	
• To further assess the humoral and cellular immune response to Ad26COVS1 in various regimens	Humoral Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1 and 3: • SARS-CoV-2 neutralization as assessed by alternative SARS-CoV-2 neutralization assays (different from the VNA used for the secondary endpoint). • Adenovirus neutralization. • Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping). • Epitope-specificity characterization for B- and T-cells. • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. Cellular Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1, 2, and 3: • Analysis of gene expression in cells stimulated with SARS-CoV-2 S protein or other SARS-CoV-2 protein peptides, or in unstimulated cells (ex vivo). • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells stimulated with SARS-CoV-2 S protein or other SARS-CoV-2 protein peptides. A subset of participants in Cohort 2 only: • Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube-isolated PBMCs).
• To perform a preliminary analysis of vaccine efficacy in the prevention of molecularly confirmed COVID-19	• The number of molecularly confirmed COVID-19 cases in Ad26COVS1 versus placebo recipients in the overall study
• To perform preliminary analysis of vaccine efficacy in the prevention of asymptomatic SARS-CoV-2 infection	• The number of participants with positive non-S protein ELISA (eg, N ELISA), if such an assay can be developed, in the Ad26COVS1 and placebo groups

Objectives	Endpoints
• To evaluate the presence of SARS-CoV-2 infection and the presence and severity of COVID-19 signs and symptoms	• Presence and severity of COVID-19 signs and symptoms • Confirmation of SARS-CoV-2 infection by molecular testing

Hypothesis

No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, reactogenicity, and immunogenicity endpoints.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, FIH Phase 1/2a multicenter study in adults aged ≥18 to ≤55 years and aged ≥65 years. The safety, reactogenicity, and immunogenicity of Ad26COVS1 will be evaluated at 2 dose levels, administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in one cohort.

The safety, reactogenicity, and immunogenicity will be first evaluated in a cohort of adults aged ≥18 to ≤55 years, followed by expansion of the selected dose and regimen in a safety cohort in this age group, which will be sufficiently large to proceed to efficacy trials if indicated. After confirmation of an acceptable safety, reactogenicity, and immunogenicity profile in the first cohort of adults aged ≥18 to ≤55 years, safety, reactogenicity and immunogenicity will be evaluated in a cohort of adults aged ≥65 years.

The study includes the following cohorts:

1) Cohort 1:
    a. Cohort 1a: 250 participants (50 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: 200 participants aged ≥18 to ≤55 years who will be randomized in parallel in a 3:1 ratio to receive the regimen of Ad26COVS1 selected from Cohort 1a (150 participants) or a placebo (50 participants). After the primary analysis for safety of the selected single- or 2-dose primary regimen, Cohort 2 will include an evaluation of a single booster vaccination (see below for further details).
3) Cohort 3: 250 participants (50 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: Vaccination Schedules

Cohort 1a (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	50	Ad26COVS1 5×10^{10} vp	Ad26COVS1 5×10^{10} vp
2	50	Ad26COVS1 5×10^{10} vp	Placebo
3	50	Ad26COVS1 1×10^{11} vp	Ad26COVS1 1×10^{11} vp
4	50	Ad26COVS1 1×10^{11} vp	Placebo
5	50	Placebo	Placebo
Cohort 1b (Adults ≥18 to ≤55 years) [a]			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	5	Ad26COVS1 5×10^{10} vp	Ad26COVS1 5×10^{10} vp
2	5	Ad26COVS1 5×10^{10} vp	Placebo
3	5	Ad26COVS1 1×10^{11} vp	Ad26COVS1 1×10^{11} vp
4	5	Ad26COVS1 1×10^{11} vp	Placebo
5	5	Placebo	Placebo
Cohort 2 (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)** [b]	**Day 57 (Vaccination 2)** [b]
1	150	Selected Ad26COVS1 dose level	Selected Ad26COVS1 dose level
2	50	Placebo	Placebo
Cohort 3 (Adults ≥65 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1 [c]	50	Ad26COVS1 5×10^{10} vp	Ad26COVS1 5×10^{10} vp
2 [c]	50	Ad26COVS1 5×10^{10} vp	Placebo
3 [c]	50	Ad26COVS1 1×10^{11} vp	Ad26COVS1 1×10^{11} vp
4 [c]	50	Ad26COVS1 1×10^{11} vp	Placebo
5 [c]	50	Placebo	Placebo
Total	**725**		

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 based on safety and immunogenicity results from the interim or primary analyses of Cohort 1a. After the primary analysis for safety of the selected single- or 2-dose primary regimen, Cohort 2 will include an evaluation of a single booster vaccination (see below for further details).

c. If only the higher dose level (1×10^{11} vp) in a 1- or 2-dose regimen meets the criteria for initiating an efficacy study based on results from Cohort 1, then the 5×10^{10} vp dose level will not be administered to participants in Cohort 3. In this case, 100 participants would be randomized to each of Groups 3 and 4, and 50 participants would be randomized to Group 5.

N = number of participants

An internal Data Review Committee (DRC) will be commissioned for this study to evaluate safety data over the course of the study and to review any events that meet a specific study pausing rule or any other safety issue that may arise.

Cohort 1 (Adults Aged ≥18 to ≤55 Years)

The first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) in Cohort 1a, enrolled at the same study site, to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. In Cohort 1a, as for each cohort, participants will be closely observed for a minimum of 30 minutes post-vaccination for the development of acute reactions. A telephone call will be made to each of these 5 sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data, which will include solicited and unsolicited AEs and SAEs. The collected data will be reviewed in a blinded manner by the Principal

Investigator (PI) and the sponsor's Study Responsible Physician (SRP). Randomization and vaccination of additional participants will be halted until the review is completed. In the absence of clinically significant findings, an additional 10 participants will be enrolled at the same study site as the 5 sentinel participants, randomly assigned to 1 of the 5 vaccination groups to have an overall 1:1:1:1:1 randomization ratio (ie, a total of 15 participants including the 5 sentinels, with 3 participants in each vaccination group), and administered the first vaccination.

The DRC will review the blinded 7-day safety data (ie, from Day 1 to Day 8) following administration of the first vaccination to the first 15 participants. Further randomization and vaccination of participants will be suspended until the DRC review is completed. Safety data for review will include solicited and unsolicited AEs and SAEs. In the absence of safety concerns, enrollment and vaccination of the remaining participants in Cohort 1a will continue and the enrollment and vaccination of participants in Cohort 1b will begin. The first 15 participants in Cohort 1a will progress to the second vaccination on Day 57. The second vaccination will be administered to the 5 sentinel participants first. The PI and SRP will also review blinded safety data from these participants following the second vaccination but randomization and vaccination of participants will not be halted during this review.

There will be 2 interim analyses of the data in Cohort 1a following the first study vaccination: interim analysis 1 examining safety data 28 days after the first study vaccination, and immunogenicity data 14 days after the first study vaccination if available based on operational considerations, and interim analysis 2 analyzing immunogenicity data 28 days after the first study vaccination.

There will also be 2 primary analyses in Cohort 1a following the second study vaccination: primary analysis 1 examining safety data at 28 days after the second study vaccination, and immunogenicity data 14 days after the second study vaccination if available based on operational considerations, and primary analysis 2 examining immunogenicity data 28 days after the second study vaccination.

Prespecified criteria may be used in the interim analyses and primary analyses of Cohort 1a to help guide selection of the optimal dose level and regimen, which will be used for Cohort 2.

Cohort 2 (Adults Aged ≥18 to ≤55 Years)

When an optimal dose level and regimen are selected based on data from Cohort 1a, vaccination of participants in Cohort 2 will be initiated with this dose level and regimen. The Th1/Th2 response will be examined before vaccination of any participant in Cohort 2. A total of 150 participants will receive the selected Ad26COVS1 regimen and 50 participants will receive a placebo. No staggered enrollment will be performed for Cohort 2; however, the DRC will evaluate safety data from Cohort 2 over the course of the study. This safety cohort will contribute to the safety database prior to initiation of larger studies.

Even if a single-dose regimen is shown to induce an acceptable immune response in an interim analysis of Cohort 1a, it may still be decided that participants in Cohort 2 will receive a second dose of Ad26COVS1 if results from the primary analyses after the second study vaccination in Cohort 1a would support this regimen.

Combined safety results through 28 days after completion of the regimen in Cohorts 1a and 2 will be used to demonstrate the safety required to initiate larger scale studies with the vaccine. Data obtained after a single booster vaccination will be used to evaluate the effect of a booster vaccination at different time points and the duration of immune response (see below for further details).

Cohort 3 (Adults Aged ≥65 Years)

Upon confirmation of an acceptable safety and immunogenicity profile (including Th1/Th2 response) of Ad26COVS1 from the interim or primary analyses of Cohort 1a, the safety and immunogenicity of Ad26COVS1 in adults aged ≥65 years will be assessed in Cohort 3.

In Cohort 3, the first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. Safety evaluations and staggered enrollment of participants in Cohort 3, including DRC review of blinded 7-day safety data following administration of the first vaccination to the first 15 participants, will proceed in the same manner as that described for Cohort 1a.

The dose level and regimen planned to be evaluated in Cohort 3 may be adjusted based on results from Cohort 1a. If only the higher dose level in a 1- or 2-dose regimen is selected from Cohort 1a, then the lower dose level will not be administered to participants in Cohort 3.

Single Booster Vaccination in Cohort 2

To gain preliminary insight into the safety and immunogenicity of a single booster vaccination, designated participants in Cohort 2 who received Ad26COVS1 for the single- or 2-dose primary regimen will receive a single booster vaccination of Ad26COVS1 at 6 months (Group 1a), 12 months (Group 1b), or 24 months (Group 1c) after completion of the primary regimen, and will receive placebo at other applicable time points. As a control, a subgroup of participants (Group 1d) who received Ad26COVS1 for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen. In addition, participants who received placebo for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen (Group 2). See the below table for further details. The same Ad26COVS1 dose level that was administered for the primary regimen will be used for the booster vaccination.

Table: Cohort 2 Vaccination Schedule – Primary Regimen and Single Booster Vaccination

		Primary Regimen		Booster Vaccination		
Group	N	Day 1 [a] (Vac 1)	Day 57 [a] (Vac 2)	+6 months [b]	+12 months [b]	+24 months [b]
1a	40	Ad26COVS1	Ad26COVS1	Ad26COVS1	Placebo	Placebo
1b	40	Ad26COVS1	Ad26COVS1	Placebo	Ad26COVS1	Placebo
1c	40	Ad26COVS1	Ad26COVS1	Placebo	Placebo	Ad26COVS1
1d	30	Ad26COVS1	Ad26COVS1	Placebo	Placebo	Placebo
2	50	Placebo	Placebo	Placebo	Placebo	Placebo
Total	**200**					

a. Study vaccine will be administered as a single-dose (Day 1) or 2-dose (Day 1 and Day 57) primary regimen based on safety and immunogenicity results from the interim or primary analyses of Cohort 1a.

b. Study vaccine (Ad26COVS1 or a placebo) will be administered at 6 months, 12 months, and 24 months after completion of the single-dose or 2-dose primary regimen. The same Ad26COVS1 dose level will be used as selected for the primary regimen.

N = number of participants; vac = vaccination.

Procedures in Case of COVID-19-like Signs and Symptoms

Participants will be provided with a booklet including a daily question on whether they are experiencing coronavirus disease-2019 (COVID-19)-like symptoms. If a participant experiences COVID-19-like symptoms (eg, cough, feverishness, dyspnea, gastrointestinal symptoms, anosmia), the following should take place:

- Participants should contact the study site at the time of symptom onset.
- Participants should collect a nasal swab at home (using available material for home swabs) as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms, and store it appropriately. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected by the participant. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab or at the study site if appropriate procedures are in place. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by rapid molecular testing using the nasal swab sample.
- Participants should complete the COVID-19 Signs and Symptoms Instrument (CSSI) and Global Impression of Severity, and record their highest body temperature daily, starting on the first day they experience symptoms, and the Global Impression of Change starting from the day after they first experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.

NUMBER OF PARTICIPANTS

Overall, a target of 725 adult male and female participants aged ≥18 to ≤55 years or ≥65 years will be randomly assigned in this study.

DOSAGE AND ADMINISTRATION

Participants will be vaccinated at the study site according to the schedule detailed in the Table above:

- Ad26COVS1 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 and 1×10^{11} vp
- Placebo: 0.9% NaCl solution

For blinding purposes, the same volume will be administered to all participants in a cohort.

IMMUNOGENICITY EVALUATIONS

Blood for evaluation of humoral and cellular immune responses will be drawn from all participants at the time points specified in the Schedule of Activities. Immunogenicity assessments may include, but are not limited to, the humoral and cellular immunogenicity assays (as available and feasible) summarized in the below table.

Table : Summary of Immunogenicity Assays

Assay	Purpose
Humoral Immunogenicity	
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 (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein and, if such an assay can be developed, SARS-CoV-2 N protein
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other strain), as measured by an alternative neutralization assay (different from the VNA used for the secondary endpoint)
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Cellular Immunogenicity	
Flow cytometry (ICS) Or ELISpot	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by ICS including $CD4^+$/$CD8^+$, IFNγ, IL-2,TNFα, IL-4, IL-5, and/or IL-13 Or IFNγ and IL-4 responses to SARS-CoV-2 S protein, and/or other SARS-CoV-2 protein peptides by PBMCs, based on dual or single ELISpot
Gene expression analysis	Analysis of gene expression by RNA transcript profiling and/or analysis of protein translates, in cells or whole blood stimulated with SARS-CoV-2 S protein, other SARS-CoV-2 protein peptides, or in unstimulated cells or whole blood (ex vivo)
Cytokine profiling (ELISA or multiplexed arrays)	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in whole blood stimulated with SARS-CoV-2 S protein, other SARS-CoV-2 protein peptides, or in unstimulated cells or whole blood by ELISA or multiplexed arrays and confirmation by functional in vitro assays
T and B cell phenotyping	Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube isolated PBMCs)

ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot (assay); ICS = intracellular cytokine staining; IFNγ = interferon gamma; Ig = immunoglobulin; IL = interleukin; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; S = spike; SARS-CoV 2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha; VNA = virus neutralization assay.

SAFETY EVALUATIONS

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. Participants will be asked to note in the 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).

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. Participants will also be instructed

on how to note signs and symptoms in the 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, and myalgia.

AEs and special reporting situations, whether serious or non-serious, 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. All other unsolicited AEs will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. All other SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) will be reported from the moment of first vaccination until completion of the participant's last study-related procedure.

STATISTICAL METHODS

Sample Size Calculation

The number of participants chosen for this study will provide a preliminary safety and immunogenicity assessment. While mild-to-moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. When 50 and 150 participants are vaccinated, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 5.8% and <2.0% respectively.

Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

FAS: The full analysis set will include all participants with at least one vaccine administration documented.

PPI: The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural infection occurring after screening (if applicable) will be excluded from the analysis set.

PPE: The per protocol efficacy population will include all randomized participants having received at least 1 vaccination for whom efficacy data concerning endpoint measures are available. All efficacy analyses will be done according to the as treated principle (ie, actually received vaccinations).

Primary Endpoint

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group. In addition, for selected tables, tabulations pooled by vaccine dose will also be provided. All safety analyses will be made on the FAS.

Secondary Endpoints

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval, or median and interquartile range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters at all available time points. Graphical representations of immunologic parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

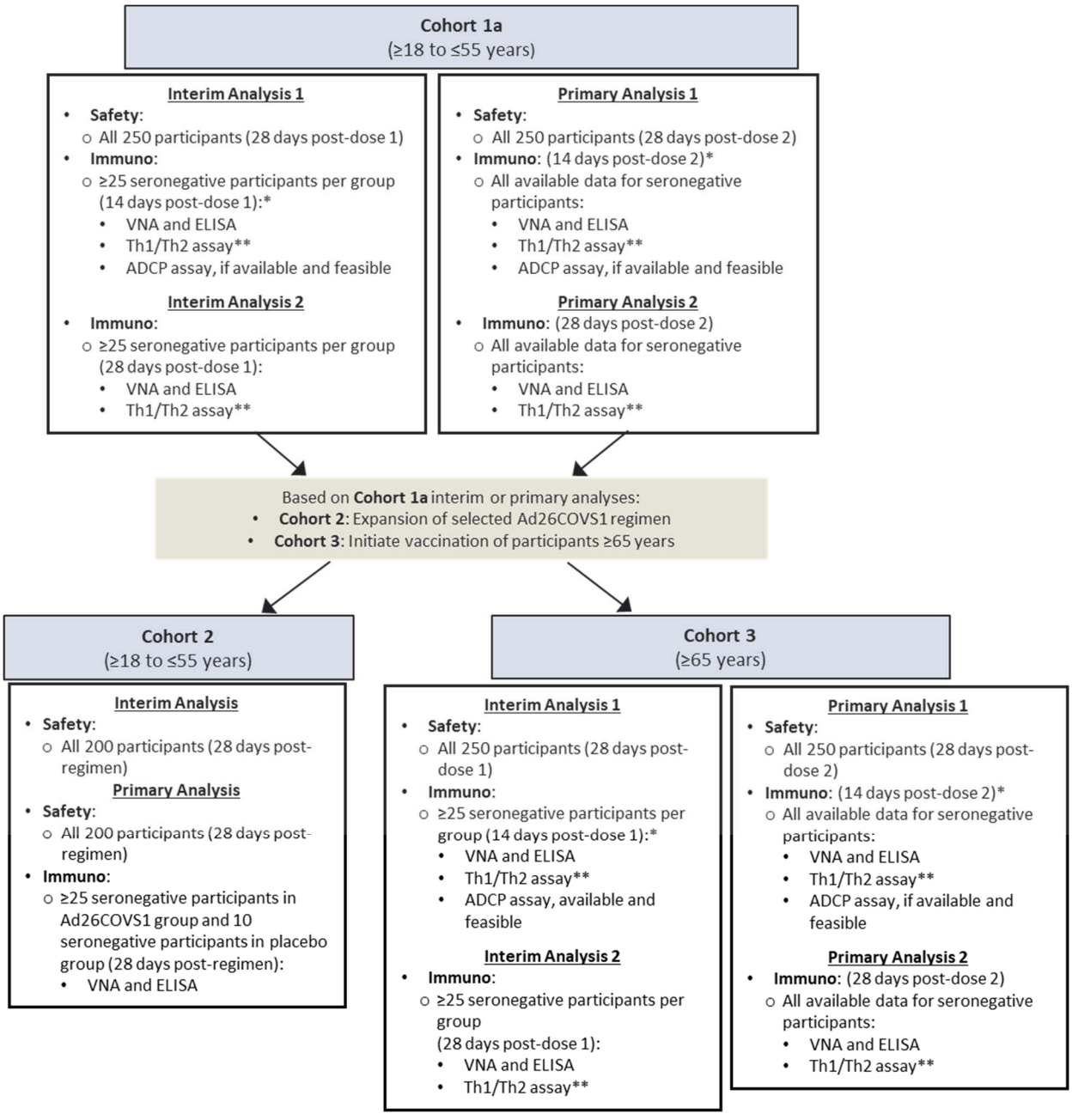
In addition, the ratio between neutralizing and binding antibodies as determined by S protein ELISA and VNA, respectively, will be calculated.

The immunogenicity analyses will be performed on the PPI population. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols).

Planned Analyses

Interim and primary analyses for each cohort are presented in the figure below.

Figure: Interim and Planned Analyses



*May be performed based on operational availability of data.
**Analysis of VNA/ELISA may be performed before availability of Th1/Th2 data, which may not be available at the time of this analysis. Vaccination of participants in Cohorts 2 or 3 will not be initiated without confirmation of a Th1-type response.
ADCP = antibody-dependent cellular phagocytosis; ELISA = enzyme-linked immunosorbent assay; Th = T-helper; VNA = virus neutralization assay

The final analysis will be performed when the last participant from Cohorts 1a and 3 completes the final visit (Visit 13, 12 months after first study vaccination) or discontinues earlier. It will include any data for Cohorts 1a and 3 that were not available for the interim and primary analyses and all data that are available for Cohorts 1b and 2 (including any data after booster vaccinations). It will also include data from participants in each cohort who were seropositive for SARS-CoV-2-specific antibodies at screening.

End-of-study Analysis

The end-of-study analysis will be performed when all included participants have completed the last visit or last booster vaccination follow-up visit, or discontinued earlier.

1.2. Schema

Figure 1: Schematic Overview of Cohorts 1 and 3

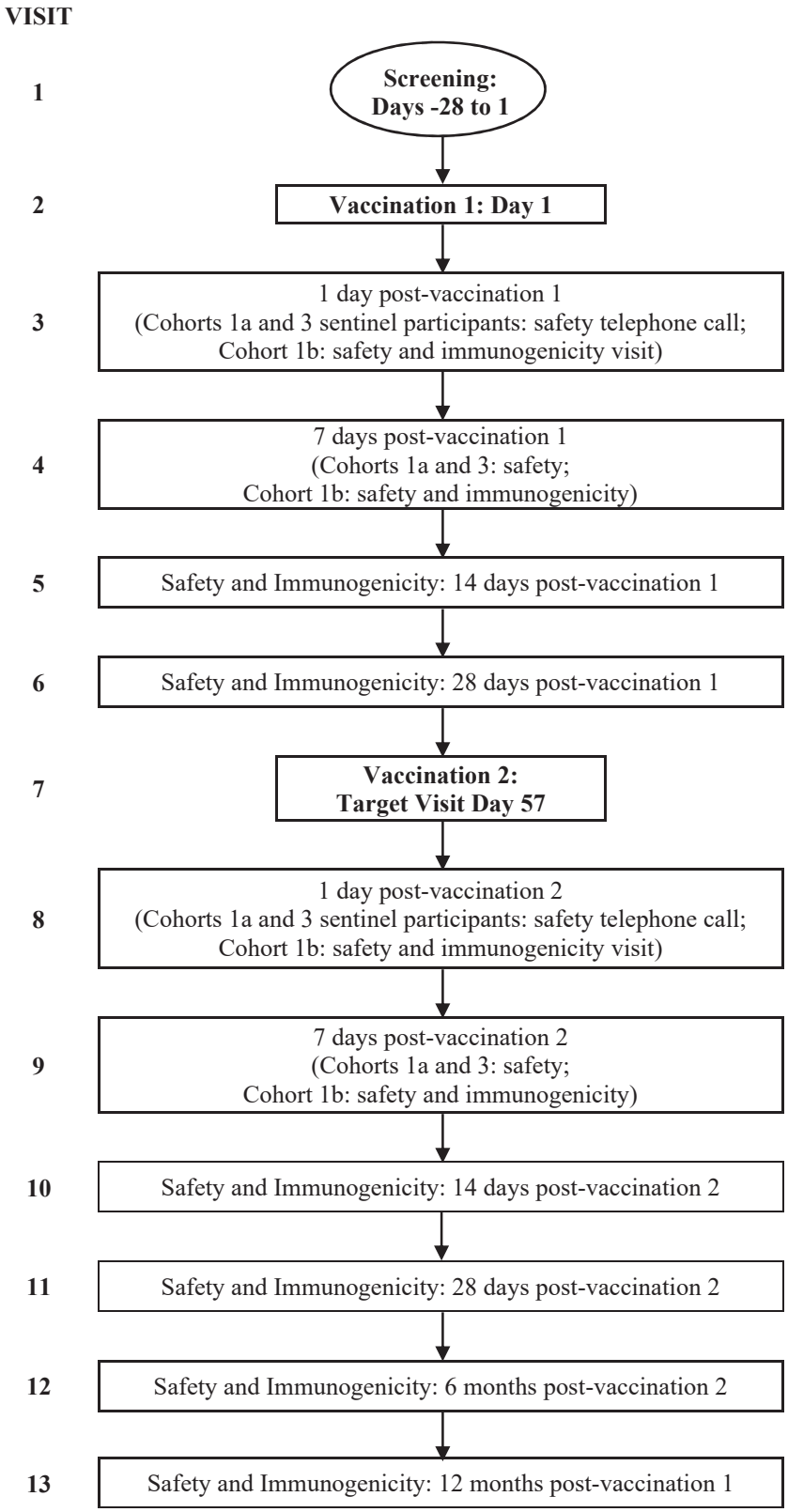
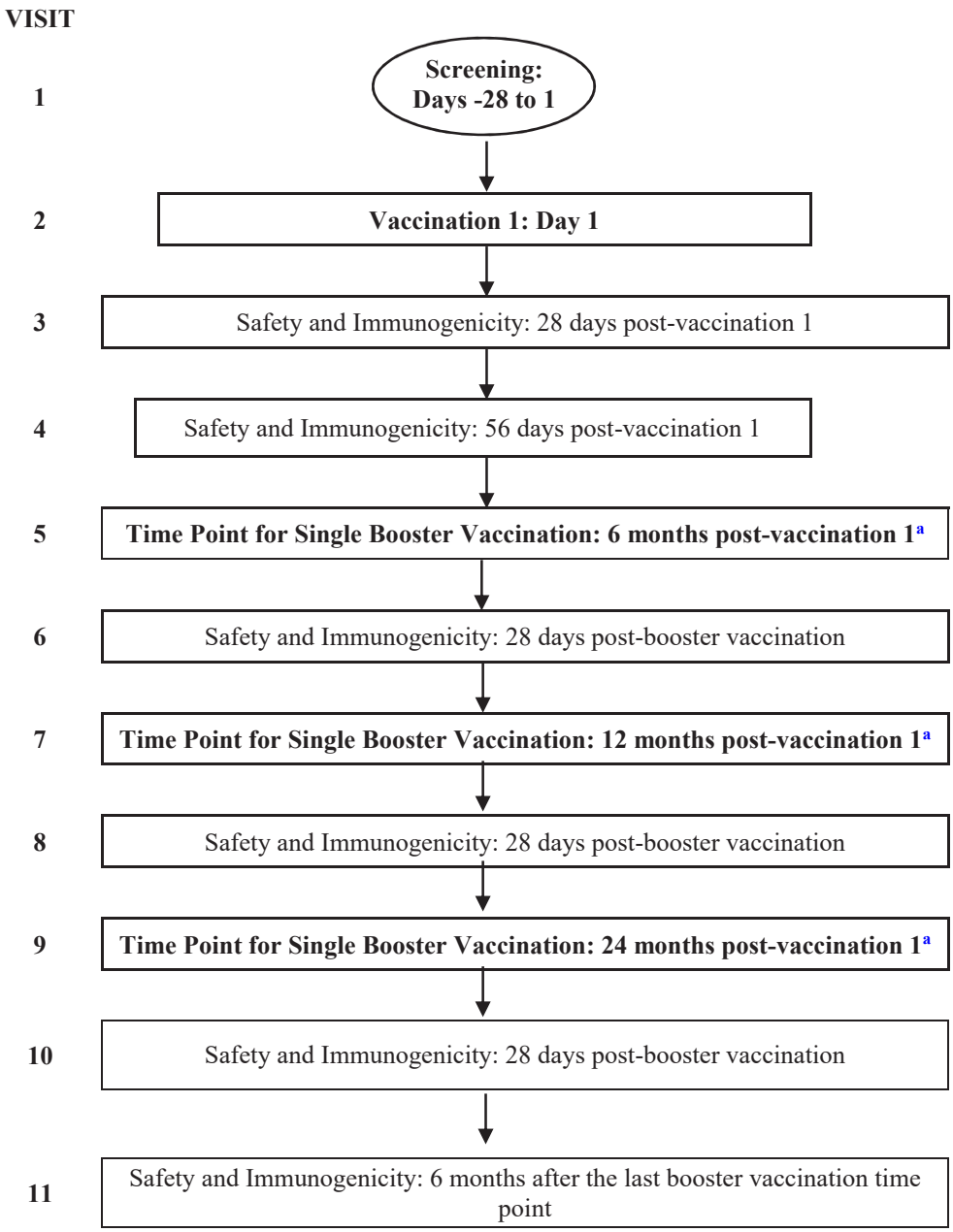
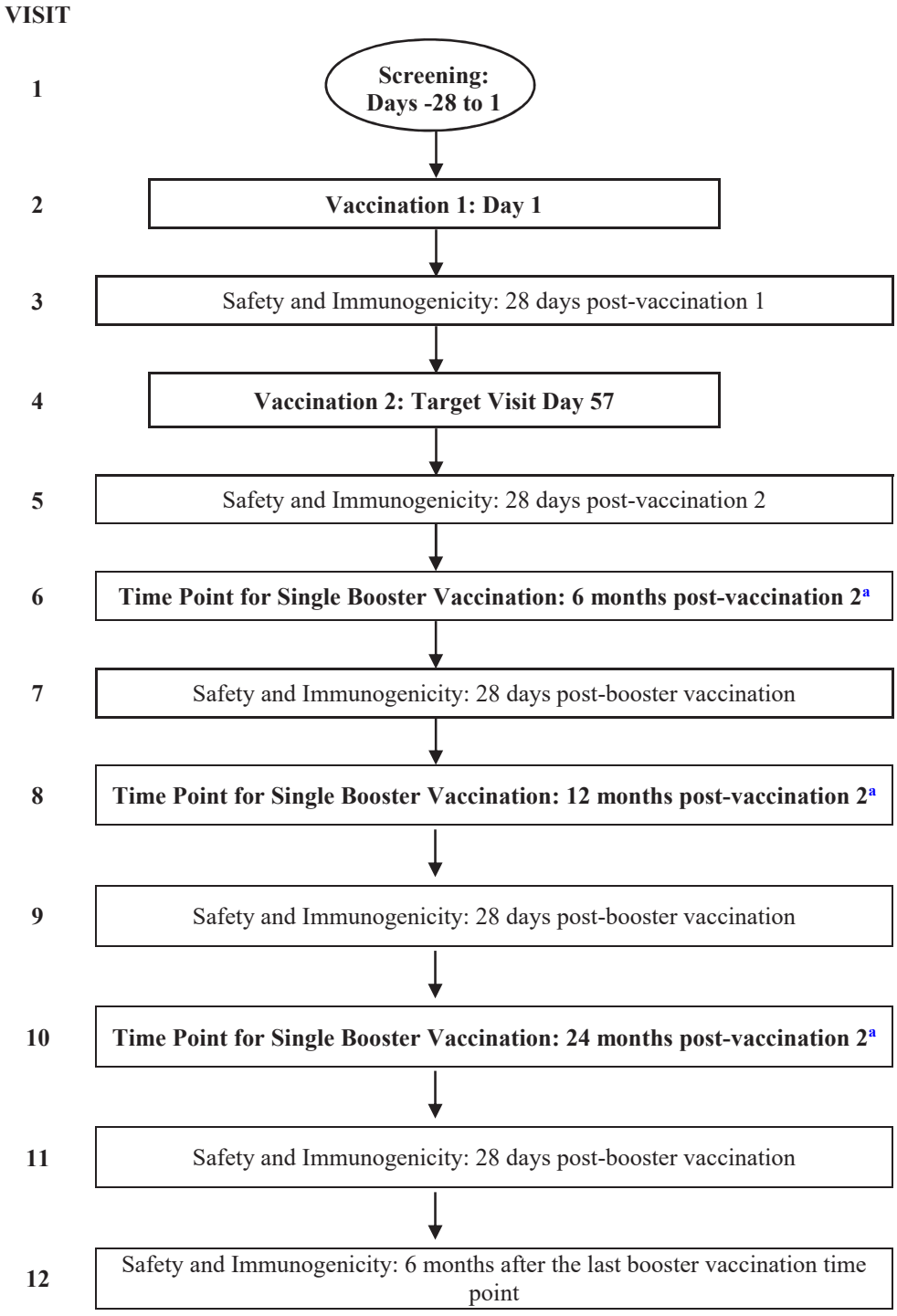


Figure 2: Schematic Overview of Cohort 2 (Single-dose Regimen)



a. Participants designated to receive a single booster vaccination will receive Ad26COVS1 at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other indicated time points. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

Figure 3: Schematic Overview of Cohort 2 (Two-dose Regimen)



a. Participants designated to receive a single booster vaccination will receive Ad26COVS1 at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other indicated time points. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

1.3. Schedule of Activities (SoA)

1.3.1. Cohort 1a

Phase	Screening [a]	Study Period												
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 1 +12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	366±21	
Visit Type	Screening	Vaccine 1	(Sentinels: safety tel.)	Safety	Safety and Immuno		Vaccine 2	(Sentinels: safety tel.)	Safety	Safety and Immuno				Early Exit
Written informed consent [d]	●													
Inclusion/exclusion criteria	●													
Demographics	●													
Medical history/prestudy meds	●	●												
Physical examination [e]	●													
Vital signs [f] incl. body temperature	●	❷		●	●	●	❷		●	●	●			❹
Nasal swab sample	❼													
Rapid serological test for SARS-CoV-2-specific antibodies, if available	●													
Randomization		❶												
Prevaccination symptoms [g]		❶					❶							
Urine pregnancy test [h]	●	❶					❶							
Hemoglobin test, mL		❶ 2												
Humoral immunity (serum), mL		❶ 30			● 30	● 30	❶ 30			● 30	● 30	● 30	● 30	❸ 20
Cellular immunity (PBMC), mL [i]		❶ 60			● 60	● 60	❶ 60			● 60	● 60	● 60	● 60	❸ 60
Cellular immunity (whole blood, PAXgene® tubes), mL [i]		❶ 2.5			● 2.5	● 2.5	❶ 2.5			● 2.5	● 2.5			
Vaccination		●					●							
30 minute post-vaccination observation [j]		●					●							
Solicited AE recording		*- - - - - Continuous- - - - -*					*- - - - - Continuous- - - - -*							❹
Unsolicited AE recording [k]		*- - - - - Continuous through +28 d- - - - -*					*- - - - - Continuous through +28 d- - - - -*							❺
SAE recording [l]		*- - - - - Continuous- - - - -*												●
Concomitant meds [m]		*- - - - - Continuous- - - - -*												●

Phase	Screening [a]	Study Period												
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 1 +12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	366±21	
Visit Type	Screening	Vaccine 1	(Sentinels: safety tel.)	Safety	Safety and Immuno		Vaccine 2	(Sentinels: safety tel.)	Safety	Safety and Immuno				Early Exit
Participant diary distribution [n]		●					●							
Participant diary review [o]			❻	●				❻	●					
Training and distribution: nasal swab kit and symptom surveillance booklet		●												
Signs and symptoms surveillance [p]		- *Continuous*- -												
Approx. daily blood draw, mL: Participants at selected sites [Participants not at selected sites]	-	94.5 [32]	- [-]	- [-]	92.5 [30]	92.5 [30]	92.5 [30]	- [-]	- [-]	92.5 [30]	92.5 [30]	90 [30]	90 [30]	80 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [Participants not at selected sites]	-	94.5 [32]	94.5 [32]	94.5 [32]	187 [62]	279.5 [92]	372 [122]	372 [122]	372 [122]	464.5 [152]	557 [182]	647 [212]	**737 [242]**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ check of diary during the telephone call for sentinel participants ❼ Screening diagnostic test for SARS-CoV-2 infection will be performed locally.

* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 13, 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).

c. If a participant comes in early for Visit 4 or 9 ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Signing of the ICF should be done before any study-related activity.

e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

f. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest . Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.
g. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 3). 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.
h. For women of childbearing potential only.
i. Samples to be taken from at least 125 participants at selected sites.
j. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.
k. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
l. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
m. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
n. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
o. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
p. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-Cov-2 = Severe acute respiratory syndrome coronavirus-2; tel = telephone contact; vac = vaccination.

1.3.2. Cohort 1b

Phase	Screening [a]	Study Period											
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 1 + 12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	366±21	
Visit Type	Screening	Vaccine 1	Safety and Immuno				Vaccine 2	Safety and Immuno						Early Exit
Written informed consent [d]	●													
Inclusion/exclusion criteria	●													
Demographics	●													
Medical history/prestudy meds	●	●												
Physical examination [e]	●													
Vital signs [f] incl. body temperature	●	❷		●	●	●	❷		●	●	●			❹
Nasal swab sample	❻													
Rapid serological test for SARS-CoV-2-specific antibodies, if available	●													
Randomization		❶												
Prevaccination symptoms [g]		❶					❶							
Urine pregnancy test [h]	●	❶					❶							
Hemoglobin test, mL		❶ 2												
Humoral immunity (serum), mL		❶ 40	● 20	● 40	● 40	● 40	❶ 20	● 20	● 40	● 40	● 40	● 20	● 20	❸ 20
Cellular immunity (PBMC), mL		❶ 60		● 60	● 60	● 60	❶ 60		● 60	● 60	● 60	● 60	● 60	❸ 60
Cellular immunity (whole blood, PAXgene® tubes), mL		❶ 2.5	● 2.5	● 2.5			❶ 2.5	● 2.5	● 2.5					
Vaccination		●					●							
30 minute post-vaccination observation [i]		●					●							
Solicited AE recording		*- - - - - Continuous- - - - -*					*- - - - - Continuous- - - - -*							❹
Unsolicited AE recording [j]		*- - - - - Continuous through +28 d- - - - -*					*- - - - - Continuous through +28 d- - - - -*							❺
SAE recording [k]		*- - - - - - - - - - - - - - - - - - - Continuous- -*												●
Concomitant meds [l]		*- Continuous- -*												●

Phase	Screening [a]	Study Period												
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Exit [b]**
Visit Timing		**Vac 1**	**Vac 1 + 1 d**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 1 d**	**Vac 2 + 7 d**	**Vac 2 + 14 d**	**Vac 2 + 28 d**	**Vac 2 + 6 mo**	**Vac 1 + 12 mo**	
Target Visit Day ±Window	**-28 to 1**	**1**	**2**	**8±2 [c]**	**15±3**	**29±3**	**57-3/+7**	**58***	**64*±2 [c]**	**71*±3**	**85*±3**	**239*±21**	**366±21**	
Visit Type	**Screening**	**Vaccine 1**	**Safety and Immuno**				**Vaccine 2**	**Safety and Immuno**						**Early Exit**
Participant diary distribution [m]		●					●							
Participant diary review [n]			●	●				●	●					
Training and distribution: nasal swab kit and symptom surveillance booklet		●												
Signs and symptoms surveillance [o]		*Continuous*												
Approx. daily blood draw, mL:	-	104.5	22.5	102.5	100	100	82.5	22.5	102.5	100	100	80	80	80
Approx. cumulative blood draw, mL:	-	104.5	127	229.5	329.5	429.5	512	534.5	637	737	837	917	**997**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ Screening diagnostic test for SARS-CoV-2 infection will be performed locally.

* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 13, 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).

c. If a participant comes in early for Visit 4 or 9 ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Signing of the ICF should be done before any study-related activity.

e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

f. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.

g. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 3). 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.
h. For women of childbearing potential only.
i. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.
j. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
k. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
l. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
m. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
n. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
o. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-Cov-2 = Severe acute respiratory syndrome coronavirus-2; vac = vaccination.

1.3.3. Cohort 2

1.3.3.1. Single-dose Primary Regimen

If a single-dose primary regimen is selected for Cohort 2, the below Schedule of Activities will be followed.

1.3.3.1.1. Primary Regimen

Phase	Screening [a]	Study Period			
Visit #	1	2	3	4	Exit [b]
Visit Timing		Vac 1	Vac 1 + 28 d	Vac 1 + 56 d	
Target Visit Day ±Window	-28 to 1	1	29±3	57-3/+7	
Visit Type	**Screening**	**Vaccine 1**	**Safety and Immuno**	**Safety and Immuno**	**Early Exit**
Written informed consent [c]	●				
Inclusion/exclusion criteria	●				
Demographics	●				
Medical history/prestudy meds	●	●			
Physical examination [d]	●				
Vital signs [e] incl. body temperature	●	❷	●	●	❹
Nasal swab sample	❻				
Rapid serological test for SARS-CoV-2-specific antibodies, if available	●				
Randomization		❶			
Prevaccination symptoms [f]		❶			
Urine pregnancy test [g]	●	❶			
Hemoglobin test, mL		❶ 2			
Humoral immunity (serum), mL		❶ 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [h]		❶ 60	● 60	● 60	❸60
Cellular immunity (whole blood, PAXgene tubes), mL [h]		❶ 2.5	● 2.5	● 2.5	
Smart Tube sample (whole blood), mL [h]		❶ 4	● 4		
Vaccination		●			
30 minute post-vaccination observation [i]		●			
Solicited AE recording [j]		*Cont +7d*			❹
Unsolicited AE recording [k]		*- - - - Continuous through +28 d- - -*			❺
SAE recording [l]		*- - - - - - - - - - - - - - - - - - Continuous- - - - - - - - - - - - - - - - - -*			●
Concomitant meds [m]		*- - - - - - - - - - - - - - - - - - Continuous- - - - - - - - - - - - - - - - - -*			●
Participant diary distribution [n]		●			
Participant diary review			●		

Phase	Screening [a]	Study Period			
Visit #	1	2	3	4	Exit [b]
Visit Timing		Vac 1	Vac 1 + 28 d	Vac 1 + 56 d	
Target Visit Day ±Window	-28 to 1	1	29±3	57-3/+7	
Visit Type	Screening	Vaccine 1	Safety and Immuno	Safety and Immuno	Early Exit
Training and distribution: nasal swab kit and symptom surveillance booklet		●			
Signs and symptoms surveillance [o]		- - - - *Continuous* - - - -			
Approx. daily blood draw, mL: 40 participants at selected sites [Other participants]		98.5 [32]	96.5 [30]	92.5 [30]	80 [20]
Approx. cumulative blood draw, mL: 40 participants at selected sites [Other participants]		98.5 [32]	195 [62]	287.5 [92]	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ Screening diagnostic test for SARS-CoV-2 infection will be performed locally.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.
b. For those participants who are unable to continue participation in the study up to Visit 4, 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).
c. Signing of the ICF should be done before any study-related activity.
d. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
e. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.
f. 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 at the scheduled time for vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor.
g. For women of childbearing potential only.
h. Samples will be collected for 40 participants at selected sites.
i. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.
j. Participants will record solicited symptoms in a diary for 7 days post-vaccination.

k. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
l. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
m. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
n. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
o. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; vac = vaccination.

1.3.3.1.2. Booster Vaccination

Phase	Study Period							
Visit #	5	6	7	8	9	10	11	Exit [a]
Visit Timing	Vac 1 + 6 mo	Booster +28 d	Vac 1 + 12 mo	Booster + 28 d	Vac 1 + 24 mo	Booster + 28 d	Booster + 6 mo	
Target Visit Day ±Window	183±21	211*±3	366±21	394*±3	731±21	759*±3	913*±21	
Visit Type	Booster [b]	Safety and Immuno	Booster [b]	Safety and Immuno	Booster [b]	Safety and Immuno	Safety and Immuno	Early Exit
Vital signs [c] incl. body temperature	❷	●	❷	●	❷	●		❺
Prevaccination symptoms [d]	❶		❶		❶			
Urine pregnancy test [e]	❶		❶		❶			
Humoral immunity (serum), mL	❶ 30	● 30	❶ 30	● 30	❶ 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [f]	❶ 60		● 60					❹60
Vaccination	●		●		●			
30 minute post-vaccination observation [g]	●		●		●			
Solicited AE recording [h]	*Cont +7d*		*Cont +7d*		*Cont +7d*			❺
Unsolicited AE recording [i]	*- - - - Continuous through +28 d- - - -*		*- - - - Continuous through +28 d- - -*		*- - - - - Continuous through +28 d- - - -*			❻
SAE recording [j]	*- Continuous- -*							●
Concomitant meds [k]	*- Continuous- -*							●
Participant diary distribution	●		●		●			
Participant diary review		●		●		●		
Signs and symptoms surveillance [l]	*- - - - - - - - - - - - Continuous- - - - - - - - - - -*							
Approx. daily blood draw, mL: 40 participants at selected sites [Other participants]	90 [30]	30 [30]	90 [30]	30 [30]	30 [30]	30 [30]	30 [30]	80 [20]
Approx. cumulative blood draw, mL: 40 participants at selected sites [Other participants]	377.5 [122]	407.5 [152]	497.5 [182]	527.5 [212]	557.5 [242]	587.5 [272]	**617.5 [302]**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood sample for humoral immunogenicity will only be taken if the early exit visit is at least 10 days after the previous humoral immunogenicity blood draw; ❹ blood sample for cellular immunogenicity will only be taken if the early exit visit coincides with or is before Visit 7 and is at least 10 days after the previous cellular immunogenicity blood draw; ❺ if within 7 days of the previous vaccination; ❻ if within 28 days of the previous vaccination.

*The timings of visits after a booster vaccination will be determined relative to the actual day of that vaccination.

a. For those participants who are unable to continue participation in the study up to Visit 11, 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).
b. Participants designated to receive a single booster vaccination will receive Ad26COVS1 at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other applicable time points. Participants not designated to receive a single booster vaccination will receive placebo at each applicable time regimen. See Table 2 for further details.
c. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.
d. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 4). 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.
e. For women of childbearing potential only.
f. Samples will be collected for 40 participants at selected sites.
g. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.
h. Participants will record solicited symptoms in a diary for 7 days post-vaccination.
i. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
j. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
k. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
l. Through 1 year after completion of the primary regimen, if a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms. At 1 year after completion of the primary regimen, the need for, and level of, surveillance and follow-up for signs and symptoms will be re-evaluated based on the status of the COVID-19 pandemic. Continued recording of signs and symptoms of COVID-19 until study end may be required.

AE = adverse event; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; vac = vaccination

1.3.3.2. Two-Dose Primary Regimen

If a 2-dose primary regimen is selected for Cohort 2, the below Schedule of Activities will be followed.

1.3.3.2.1. Primary Regimen

Phase	Screening [a]	Study Period				
Visit #	1	2	3	4	5	Exit [b]
Visit Timing		Vac 1	Vac 1 + 28 d	Vac 2	Vac 2 + 28 d	
Target Visit Day ±Window	-28 to 1	1	29±3	57-3/+7	85*±3	
Visit Type	Screening	Vaccine 1	Safety and Immuno	Vaccine 2	Safety and Immuno	Early Exit
Written informed consent [c]	●					
Inclusion/exclusion criteria	●					
Demographics	●					
Medical history/prestudy meds	●	●				
Physical examination [d]	●					
Vital signs [e] incl. body temperature	●	❷	●	❷	●	❹
Nasal swab sample	❻					
Rapid serological test for SARS-CoV-2-specific antibodies, if available	●					
Randomization		❶				
Prevaccination symptoms [f]		❶		❶		
Urine pregnancy test [g]	●	❶				
Hemoglobin test		❶ 2				
Humoral immunity (serum), mL		❶ 30	● 30	❶ 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [h]		❶ 60	● 60	❶ 60	● 60	❸60
Cellular immunity (whole blood, PAXgene tubes), mL [h]		❶ 2.5	● 2.5	❶ 2.5	● 2.5	
Smart Tube sample (whole blood), mL [h]		❶ 4	● 4			
Vaccination		●		●		
30 minute post-vaccination observation [i]		●		●		
Solicited AE recording [j]		*Cont +7d*		*Cont +7d*		❹
Unsolicited AE recording [k]		*- - - - Continuous through +28 d- - -*		*-- - - Continuous through +28 d- - -*		❺
SAE recording [l]		*- Continuous- -*				●
Concomitant meds [m]		*- Continuous- -*				●
Participant diary distribution [n]		●		●		
Participant diary review			●		●	

Phase	Screening [a]	Study Period				
Visit #	1	2	3	4	5	Exit [b]
Visit Timing		Vac 1	Vac 1 + 28 d	Vac 2	Vac 2 + 28 d	
Target Visit Day ±Window	-28 to 1	1	29±3	57-3/+7	85*±3	
Visit Type	Screening	Vaccine 1	Safety and Immuno	Vaccine 2	Safety and Immuno	Early Exit
Training and distribution: nasal swab kit and symptom surveillance booklet		●				
Signs and symptoms surveillance [o]		*Continuous*				
Approx. daily blood draw, mL: 40 participants at selected sites [Other participants]		98.5 [32]	96.5 [30]	92.5 [30]	92.5 [30]	80 [20]
Approx. cumulative blood draw, mL: 40 participants at selected sites [Other participants]		98.5 [32]	195 [62]	287.5 [92]	380 [122]	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ Screening diagnostic test for SARS-CoV-2 infection will be performed locally.

* The timings of the visit after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 5, 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).

c. Signing of the ICF should be done before any study-related activity.

d. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

e. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.

f. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 5). 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.

g. For women of childbearing potential only.

h. Samples will be collected for 40 participants at selected sites.

i. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.

j. Participants will record solicited symptoms in a diary for 7 days post-vaccination.

k. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
l. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
m. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
n. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
o. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; vac = vaccination

1.3.3.2.2. Booster Vaccination

Phase	Study Period							
Visit #	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Exit** [a]
Visit Timing	**Vac 2 + 6 mo**	**Booster +28 d**	**Vac 2 + 12 mo**	**Booster + 28 d**	**Vac 2 + 24 mo**	**Booster + 28 d**	**Booster + 6 mo**	
Target Visit Day ±Window	**239*±21**	**267*±3**	**422*±21**	**450*±3**	**787*±21**	**815*±3**	**969*±21**	
Visit Type	**Booster** [b]	**Safety and Immuno**	**Booster** [b]	**Safety and Immuno**	**Booster** [b]	**Safety and Immuno**	**Safety and Immuno**	**Early Exit**
Vital signs [c] incl. body temperature	❷	●	❷	●	❷	●		❺
Prevaccination symptoms [d]	❶		❶		❶			
Urine pregnancy test [e]	❶		❶		❶			
Humoral immunity (serum), mL	❶ 30	● 30	❶ 30	● 30	❶ 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [f]	❶ 60		● 60					❹60
Vaccination	●		●		●			
30 minute post-vaccination observation [g]	●		●		●			
Solicited AE recording [h]	*Cont +7d*		*Cont +7d*		*Cont +7d*			❺
Unsolicited AE recording [i]	- - - - - *Continuous through +28 d*- - - - -		- - - - - *Continuous through +28 d*- - - -		- - - - - *Continuous through +28 d*- - - -			❻
SAE recording [j]	- *Continuous*- -							●
Concomitant meds [k]	- *Continuous*- -							●
Participant diary distribution	●		●		●			
Participant diary review		●		●		●		
Signs and symptoms surveillance [l]	- - - - - - - - - - - - *Continuous*- - - - - - - - -							
Approx. daily blood draw, mL: 40 participants at selected sites [Other participants]	90 [30]	30 [30]	90 [30]	30 [30]	30 [30]	30 [30]	30 [30]	80 [20]
Approx. cumulative blood draw, mL: 40 participants at selected sites [Other participants]	470 [152]	500 [182]	590 [212]	620 [242]	650 [272]	680 [302]	**710 [332]**	

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood sample for humoral immunogenicity will only be taken if the early exit visit is at least 10 days after the previous humoral immunogenicity blood draw; ❹ blood sample for cellular immunogenicity will only be taken if the early exit visit coincides with or is before Visit 8 and at least 10 days after the previous cellular immunogenicity blood draw; ❺ if within 7 days of the previous vaccination; ❻ if within 28 days of the previous vaccination.

*The timings of visits after the second vaccination or a booster vaccination will be determined relative to the actual day of that vaccination.

a. For those participants who are unable to continue participation in the study up to Visit 12, 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).

b. Participants designated to receive a single booster vaccination will receive Ad26COVS1 at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other applicable time points. Participants not designated to receive a single booster vaccination will receive placebo at each applicable time point. See Table 2 for further details.
c. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.
d. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 5). 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.
e. For women of childbearing potential only.
f. Samples will be collected for 40 participants at selected sites.
g. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.
h. Participants will record solicited symptoms in a diary for 7 days post-vaccination.
i. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
j. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
k. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
l. Through 1 year after completion of the primary regimen, if a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms. At 1 year after completion of the primary regimen, the need for, and level of, surveillance and follow-up for signs and symptoms will be re-evaluated based on the status of the COVID-19 pandemic. Continued recording of signs and symptoms of COVID-19 until study end may be required.

AE = adverse event; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; vac = vaccination

1.3.4. Cohort 3

Phase	Screening [a]	Study Period												
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Exit [b]**
Visit Timing		**Vac 1**	**Vac 1 + 1 d**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 1 d**	**Vac 2 + 7 d**	**Vac 2 + 14 d**	**Vac 2 + 28 d**	**Vac 2 + 6 mo**	**Vac 1 + 12 mo**	
Target Visit Day ±Window	**-28 to 1**	**1**	**2**	**8±2 [c]**	**15±3**	**29±3**	**57-3/+7**	**58***	**64*±2 [c]**	**71*±3**	**85*±3**	**239*± 21**	**366±2 1**	
Visit Type	**Screening**	**Vaccine 1**	**(Sentinels: safety tel.)**	**Safety**	**Safety and Immuno**		**Vaccine 2**	**(Sentinels: safety tel.)**	**Safety**	**Safety and Immuno**				**Early Exit**
Written informed consent [d]	●													
Inclusion/exclusion criteria	●													
Demographics	●													
Medical history/prestudy meds	●	●												
Physical examination [e]	●													
Vital signs [f] incl. body temperature	●	❷		●	●	●	❷		●	●	●			❹
Nasal swab sample	❼													
Rapid serological test for SARS-CoV-2-specific antibodies, if available	●													
Randomization		❶												
Prevaccination symptoms [g]		❶					❶							
Hemoglobin test		❶ 2												
Humoral immunity (serum), mL		❶ 30			● 30	● 30	❶ 30			● 30	● 30	● 30	● 30	❸ 20
Cellular immunity (PBMC), mL, [h]		❶ 60			● 60	● 60	❶ 60			● 60	● 60	● 60	● 60	❸ 60
Cellular immunity (whole blood, PAXgene® tubes), mL, [h]		❶ 2.5			● 2.5	● 2.5	❶ 2.5			● 2.5	● 2.5			
Vaccination		●					●							
30 minute post-vaccination observation [i]		●					●							
Solicited AE recording		*- - - - - Continuous- - - - -*					*- - - - - Continuous- - - - -*							❹
Unsolicited AE recording [j]		*- - - - - Continuous through +28 d- - - - -*					*- - - - - Continuous through +28 d- - - - -*							❺
SAE recording [k]		*- - - - - Continuous- - - - -*												●
Concomitant meds [l]		*- - - - - Continuous- - - - -*												●

Phase	Screening [a]	Study Period												
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Exit [b]**
Visit Timing		**Vac 1**	**Vac 1 + 1 d**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 1 d**	**Vac 2 + 7 d**	**Vac 2 + 14 d**	**Vac 2 + 28 d**	**Vac 2 + 6 mo**	**Vac 1 + 12 mo**	
Target Visit Day ±Window	**-28 to 1**	**1**	**2**	**8±2 [c]**	**15±3**	**29±3**	**57-3/+7**	**58***	**64*±2 [c]**	**71*±3**	**85*±3**	**239*± 21**	**366±2 1**	
Visit Type	**Screening**	**Vaccine 1**	**(Sentinels: safety tel.)**	**Safety**	**Safety and Immuno**		**Vaccine 2**	**(Sentinels: safety tel.)**	**Safety**	**Safety and Immuno**				**Early Exit**
Participant diary distribution [m]		●					●							
Participant diary review [n]			❻	●				❻	●					
Training and distribution: nasal swab kit and symptom surveillance booklet		●												
Signs and symptoms surveillance [o]		*- Continuous- -*												
Approx. daily blood draw, mL Participants at selected sites [Participants not at selected sites]	-	94.5 [32]	-	-	92.5 [30]	92.5 [30]	92.5 [30]	-	-	92.5 [30]	92.5 [30]	90 [30]	90 [30]	80 [20]
Approx. cumulative blood draw, mL Participants at selected sites [Participants not at selected sites]	-	94.5 [32]	94.5 [32]	94.5 [32]	187 [62]	279.5 [92]	372 [122]	372 [122]	372 [122]	464.5 [152]	557 [182]	647 [212]	**737 [242]**	

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ check of diary during the telephone call for sentinel participants; ❼ Screening diagnostic test for SARS-CoV-2 infection will be performed locally.

* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 13, 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).

c. If a participant comes in early for Visit 4 or 9 ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Signing of the ICF should be done before any study-related activity.
e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
f. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures will be measured preferably via the oral route.
g. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 3). 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.
h. Samples to be taken from at least 125 participants at selected sites.
i. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 30-minute post-vaccination observation period is complete.
j. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
k. All SAEs 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 first vaccination until completion of the participant's last study-related procedure.
l. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
m. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
n. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
o. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.5, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; SAE = serious adverse event; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; tel = telephone contact; vac = vaccination

1.3.5. Procedures for Participants with COVID-19-like Signs and Symptoms

Timing relative to onset of signs and symptoms	Day 1	Days 1-4	Days 3-8	From onset until resolution
Participant to contact study site as soon as any signs or symptoms of possible COVID-19 occur	●			
Nasal swab [a]		●	❶	
Body temperature [b]	❷			
COVID-19 Signs and Symptoms Instrument (CSSI) [c]	❷			
Global Impression of Severity (GIS) [c]	❷			
Global Impression of Change (GIC) [c]		❷		
Study-site personnel to contact participant [d]	*Weekly or more frequently*			

❶ A second nasal swab will be obtained 2 to 4 days after the first swab. ❷ If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.

a. Participants should collect a nasal swab at home (using available material for home swabs) as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms. The sample should be transferred to the study site by an appropriate method as soon as possible after collection by the participant.
b. Participant should measure body temperature daily and record the highest temperature each day.
c. Participants should complete the CSSI and GIS starting on the first day they experience symptoms, and the GIC starting from the day after they first experience symptoms.
d. If a participant has a positive test result for SARS-CoV 2 infection, the participant may be requested to remain at home and not visit the study site. If necessary, study site personnel will visit the participant at home. 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.

COVID-19 = coronavirus disease-2019; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2.

2. INTRODUCTION

Ad26COVS1 is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus spike (S) protein, which will be assessed in this study. This will be the first-in-human (FIH) study for Ad26COVS1.

For the most comprehensive nonclinical and clinical information regarding Ad26COVS1, refer to the latest version of the Investigator's Brochure (IB) for Ad26COVS1.[24]

The term “study vaccine” throughout the protocol, refers to Ad26COVS1 or a placebo as defined in Section 6.1, Study Vaccinations Administered. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "participant" throughout the protocol refers to the common term "subject".

COVID-19 Vaccine and Considerations

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

Although the quantitative correlate of protection against SARS-CoV-2 infection has not yet been identified, neutralizing antibody responses against the SARS-CoV and MERS S protein have been associated with protection against experimental SARS-CoV and MERS infection in nonclinical models.[12,47] 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.[31,33,48] 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 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, Risks Related to Study Participation).

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 one 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), Fc-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP) (HIV, Malaria). Furthermore, these data support an immunogenicity profile with emphasis on T-helper (Th)1 responses and demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in $CD4^+$ and $CD8^+$ T cells.[4,25,35]

Ad26COVS1 Candidate Vaccine

The aim of the COVID-19 vaccine clinical development program is to develop a safe and efficacious vaccine for the prevention of COVID-19. The initial effort will be to rapidly demonstrate safety and immunogenicity in adults aged ≤55 years, in order to initiate an efficacy trial 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 Ad26COVS1, which is a recombinant, replication-incompetent Ad26 encoding a 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). The selection of antigen was based on previous work on the SARS-CoV and MERS candidate vaccines.[12,19,36] The 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.[49]

2.1. Study Rationale

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[15,46] It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019.[32] Epidemiological investigations indicated 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.[32] 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.[33,46] 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-like coronaviruses previously sampled from bats in China.[33]

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 January 30, 2020, and declared the outbreak to be a pandemic on March 11, 2020.[43,44] As of April 19, 2020, approximately 2,347,000 cases of COVID-19 have been reported.[26]

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.[8] Severe clinical presentations have been reported in as many as 20–25% of laboratory-confirmed cases.[18] 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%).[11] 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%).[40] 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 because of complications, including acute respiratory distress syndrome, arrhythmia, and shock. At present, it appears that individuals aged 65 years or older, especially those with comorbid diseases, are subject to the highest incidence of morbidity and mortality.[9] 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.[17] 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).

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: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which have nucleotide sequence identity with SARS-CoV-2 of approximately 79% and 50%, respectively.[33] The first known cases of SARS occurred in Southern China in November 2002.[45] 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.[49] MERS-CoV is considered to be a zoonotic virus capable of non-sustained 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.[10,49] 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 8098 SARS cases and 774 deaths (case-fatality rate: 10%) with substantial social, economic and health service disruption in some affected countries.[10,45] The case-fatality rate of MERS-CoV infections is estimated to be 35%.[10]

Therefore, while the understanding of the epidemiology and clinical spectrum of COVID-19 is still evolving during the ongoing pandemic, the current knowledge of the disease burden highlights the urgent medical need for a prophylactic vaccine.

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 Phase 1/2a clinical study. Details of the nonclinical immunogenicity of Ad26COVS1 are provided in the IB.[24]

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, ie, Ad26.ENVA.01, and an Ad26-based RSV vaccine, ie, Ad26.RSV.preF. In the available biodistribution studies, the Ad26 vector did not widely distribute following IM administration in rabbits. Ad26 vector 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 profile 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 Ad26COVS1 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 (HPV), 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).

Clinical Studies

No clinical data with the Ad26COVS1 vaccine are currently available as this will be the first-in-human 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, and filovirus.

At a cutoff date of 27 March 2020, Ad26-based vaccines have been administered to more than 67,000 participants, including more than 50,000 participants in 2 large Ebola vaccination campaigns in the Democratic Republic of the Congo (VAC52150EBL3008/DRC-EB-001) and Rwanda (UMURINZI Ebola Vaccine Program campaign).

The sponsor's adenoviral vaccine (AdVac®) safety database report (V5.0, dated 10 April 2020, cutoff date 20 December 2019) describes safety data from 26 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 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 (ie, the highest dose level tested).

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, Risks Related to Study Participation 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 with participants aged ≥60 years, including the Phase 1 studies VAC18193RSV1003 and VAC18193RSV1005, Phase 1/2a study VAC18193RSV1004, Phase 2a study VAC18193RSV2003, and the Phase 2b study VAC18193RSV2001. Up to a cutoff date of 27 October 2019, more than 3,600 participants aged ≥60 years received an Ad26.RSV.preF-based regimen in completed and ongoing studies. An acceptable safety and tolerability 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.

T-helper (Th)1/Th2 Profile of Ad26-based Vaccines in Clinical Studies

In the 1960s, a formalin-inactivated (FI) 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.[14,20,27,28] 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.[37] Vaccine-induced ERD has also been described for SARS-CoV and MERS-CoV in animal models.[38]

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 interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) production in CD4+ and CD8+ T cells.[3,4,5] 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 primary analysis 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 Ad26COVS1 may be found in the IB.[24]

2.3.1. Risks Related to Study Participation

This clinical study is a FIH study for Ad26COVS1. The following potential risks will be monitored during the study and are specified in the protocol:

Risks Related to Ad26COVS1

As this will be the FIH study for Ad26COVS1, no clinical data are available to date. For the most comprehensive nonclinical information regarding Ad26COVS1, refer to the latest version of the IB.[24]

Risks Related to Adenoviral-vectored Vaccines

The clinical AdVac® safety database (report version 5.0, dated 10 April 2020, cutoff 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 (respiratory syncytial virus [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, Background, only data for approximately 230 participants aged ≥60 years from studies VAC18193RSV1003, VAC18193RSV2003, and VAC18193RSV1005 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, in 29.8% of children aged 4-11, and in 24.8% of children aged 12-17 years after vaccination with an Ad26-based vaccine. For placebo, these percentages were 29.2% in children aged 4-11 years and 14.3% in children aged 12-17 years. No children aged 1-3 years have received placebo.

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

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 1-3 years were decreased appetite (13.9%), decreased activity (13.2%), pyrexia (11.1%), and irritability (10.4%). The most frequently experienced solicited systemic AEs in children aged 4-11 years (reported in ≥15% of Ad26 participants) were headache (23.6%; no data are available for the placebo arm 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 experienced solicited systemic AEs in children aged 12-17 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.

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).

In children for Ad26, the most frequently reported unsolicited AE was malaria,[a] reported in 36.8% of children aged 1-3 years, in 19.0% of children aged 4-11 years, and in 10.6% of children aged 12-17 years. One child in the 12-17 years group (4.8%) experienced malaria after placebo vaccination. There were no other children in the placebo groups who experienced malaria. The most frequently experienced related unsolicited AE was hypernatremia (1.6% of children aged 4-11 years [vs. 4.2% with placebo] and 2.4% of children aged 12-17 years [vs. 4.8% with placebo]). No AEs in children aged 1-3 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 a 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 allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine) will be excluded from the study.

After each vaccination, participants will remain at the study site for at least 30 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

Pregnancy and Birth Control

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

Women 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 signing the informed consent form (ICF) until 3 months after the last dose of study vaccine (See Section 5.1, Inclusion Criteria). Women who are pregnant or breast-feeding will be excluded from the study. Women who become pregnant while enrolled in the study will not receive further study vaccine

[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.

but may continue other study procedures at the discretion of the investigator (see Section 7.1, Discontinuation of Study Vaccine).

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 Swabs

Collection of a nasal swab 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,[2,7,16,22,23] 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 has the potential to 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 ICF. The initial cohort in this study (Cohort 1a) will include healthy adults aged ≥18 to ≤55 years of age. Furthermore, 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 8.1.1).

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 Ad26COVS1 have yet to be established. Currently, there are no effective vaccines for 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, Study Population) 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 Schedule of Activities.
  - After each vaccination, participants will remain at the study site for at least 30 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a diary to document solicited signs and symptoms. Details are provided in Section 8.2, Safety Assessments and Section 8.3, Adverse Events and Serious Adverse Events.
  - The investigator or the designee will document unsolicited adverse events (AEs) as indicated in Section 8.2, Safety Assessments, Section 8.3, Adverse Events and Serious Adverse Events, and Section 10.3, Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.
  - 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.

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - In Cohorts 1a and 3, five sentinel participants will be evaluated for safety before extending enrollment in each cohort. The sentinel participants will be vaccinated at least 1 hour apart. A telephone call will be made to each of the sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data. The blinded 24-hour post-vaccination safety data in these sentinel participants will be reviewed by the principal investigator (PIs) and sponsor's study responsible physician (SRP). Randomization and vaccination of additional participants will be halted until this 24-hour sentinel safety evaluation is completed. In the absence of clinically significant findings, an additional 10 participants will be enrolled at the same study site, randomly assigned to the vaccination groups as described in Section 4.1, Overall Design, and administered the first vaccination. For Cohorts 1a and 3, the second vaccination will be administered to the sentinel participants first. The PI and SRP will also review blinded safety data from these participants following the second vaccination but randomization and vaccination of participants will not be halted during this review.
  - For Cohorts 1a and 3, an internal Data Review Committee (DRC) will review blinded[a] 7-day safety data following administration of the first vaccination to the first 15 participants. Further randomization and vaccination of participants will be suspended until the DRC review is completed and will only take place in the absence of safety concerns from the DRC review.
  - There are prespecified rules for all participants, that if met would result in pausing of further vaccinations, preventing exposure of new participants to study vaccine until the DRC

[a] The DRC will review blinded data first but may review unblinded data if deemed necessary.

reviews all safety data (see Committees Structure in Section 10.2, Appendix 2, Regulatory, Ethical, and Study Oversight Considerations).

- Study vaccinations will be discontinued in participants for the reasons included in Section 7, Discontinuation of Study Vaccination and Participant Discontinuation/Withdrawal.
- Contraindications to vaccination are included in Section 5.5, Criteria for Temporarily Delaying Study Vaccine Administration.

3. OBJECTIVES AND ENDPOINTS

A description of study cohorts is provided in Section 4.1.

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26COVS1 at 2 dose levels, 5×10^{10} vp and 1×10^{11} vp, administered intramuscularly (IM) as a single-dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	All participants in Cohorts 1, 2, and 3: • Solicited local and systemic adverse events (AEs) for 7 days after each vaccination • Unsolicited AEs for 28 days after each vaccination • Serious adverse events (SAEs) throughout the study (from first vaccination until end of the study; SAEs occurring before the first vaccination will be summarized separately).

Objectives	Endpoints
Secondary	
• To assess the humoral and cellular immune response to Ad26COVS1	Humoral Immune Response All participants in Cohorts 1, 2, and 3: • SARS-CoV-2 neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay (VNA [wild-type virus and/or pseudovirion expressing S protein]) • SARS-CoV-2-binding antibodies measured by enzyme-linked immunosorbent assay (ELISA): Analysis of antibodies binding to the SARS-CoV-2 S protein. Cellular Immune Response A subset of participants in Cohorts 1, 2, and 3: • Th1 and Th2 immune responses as assessed by: o Flow cytometry after SARS-CoV-2 S protein peptide stimulation of peripheral blood mononuclear cells (PBMC) and intracellular staining [ICS] including CD4+/CD8+, interferon gamma [IFNγ], interleukin [IL]-2, tumor necrosis factor alpha [TNFα], IL-4, IL-5, IL-13, and/or other Th1/Th2 markers. Or o Dual or single IFNγ and IL-4 enzyme-linked immunospot (ELISpot) assay after stimulation of PBMC with SARS-CoV-2 S protein peptides.

Objectives	Endpoints
Exploratory	
• To further assess the humoral and cellular immune response to Ad26COVS1 in various regimens	Humoral Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1 and 3: • SARS-CoV-2 neutralization as assessed by alternative SARS-CoV-2 neutralization assays (different from the VNA used for the secondary endpoint). • Adenovirus neutralization. • Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping). • Epitope-specificity characterization for B- and T-cells. • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. Cellular Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1, 2, and 3: • Analysis of gene expression in cells stimulated with SARS-CoV-2 S protein or other SARS-CoV-2 protein peptides, or in unstimulated cells (ex vivo). • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells stimulated with SARS-CoV-2 S protein or other SARS-CoV-2 protein peptides. A subset of participants in Cohort 2 only: • Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube-isolated PBMCs).
• To perform a preliminary analysis of vaccine efficacy in the prevention of molecularly confirmed COVID-19	• The number of molecularly confirmed COVID-19 cases in Ad26COVS1 versus placebo recipients in the overall study
• To perform preliminary analysis of vaccine efficacy in the prevention of asymptomatic SARS-CoV-2 infection	• The number of participants with positive non-S protein ELISA (eg, N ELISA), if such an assay can be developed, in the Ad26COVS1 and placebo groups

Objectives	Endpoints
• To evaluate the presence of SARS-CoV-2 infection and the presence and severity of COVID-19 signs and symptoms	• Presence and severity of COVID-19 signs and symptoms • Confirmation of SARS-CoV-2 infection by molecular testing

HYPOTHESIS

No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, reactogenicity, and immunogenicity endpoints (see Section 9.4, Statistical Analyses).

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, FIH Phase 1/2a multicenter study in adults aged ≥18 to ≤55 years and aged ≥65 years. The safety, reactogenicity, and immunogenicity of Ad26COVS1 will be evaluated at 2 dose levels, administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in one cohort.

The safety, reactogenicity, and immunogenicity will be first evaluated in a cohort of adults aged ≥18 to ≤55 years, followed by expansion of the selected dose and regimen in a safety cohort in this age group, which will be sufficiently large to proceed to efficacy trials if indicated. After confirmation of an acceptable safety, reactogenicity, and immunogenicity profile in the first cohort of adults aged ≥18 to ≤55 years, safety, reactogenicity and immunogenicity will be evaluated in a cohort of adults aged ≥65 years. Overall, a target of 725 adult male and female participants in these 2 age groups will be randomly assigned in this study.

Participants will receive IM injections of Ad26COVS1 or a placebo as shown in Table 1 and Table 2. Two dose levels of Ad26COVS1 will be administered: 5×10^{10} vp and 1×10^{11} vp.

The study includes the following cohorts:

1) Cohort 1:
   a. Cohort 1a: 250 participants (50 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: 200 participants aged ≥18 to ≤55 years who will be randomized in parallel in a 3:1 ratio to receive the regimen of Ad26COVS1 selected from Cohort 1a (150 participants) or a placebo (50 participants). After the primary analysis for safety of the selected single- or 2-dose primary regimen, Cohort 2 will include an evaluation of a single booster vaccination (see below for further details).

3) Cohort 3: 250 participants (50 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

Cohort 1a (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	50	Ad26COVS1 5×10^{10} vp	Ad26COVS1 5×10^{10} vp
2	50	Ad26COVS1 5×10^{10} vp	Placebo
3	50	Ad26COVS1 1×10^{11} vp	Ad26COVS1 1×10^{11} vp
4	50	Ad26COVS1 1×10^{11} vp	Placebo
5	50	Placebo	Placebo
Cohort 1b (Adults ≥18 to ≤55 years) [a]			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1	5	Ad26COVS1 5×10^{10} vp	Ad26COVS1 5×10^{10} vp
2	5	Ad26COVS1 5×10^{10} vp	Placebo
3	5	Ad26COVS1 1×10^{11} vp	Ad26COVS1 1×10^{11} vp
4	5	Ad26COVS1 1×10^{11} vp	Placebo
5	5	Placebo	Placebo
Cohort 2 (Adults ≥18 to ≤55 years)			
Group	**N**	**Day 1 (Vaccination 1)** [b]	**Day 57 (Vaccination 2)** [b]
1	150	Selected Ad26COVS1 dose level	Selected Ad26COVS1 dose level
2	50	Placebo	Placebo
Cohort 3 (Adults ≥65 years)			
Group	**N**	**Day 1 (Vaccination 1)**	**Day 57 (Vaccination 2)**
1 [c]	50	Ad26COVS1 5×10^{10} vp	Ad26COVS1 5×10^{10} vp
2 [c]	50	Ad26COVS1 5×10^{10} vp	Placebo
3 [c]	50	Ad26COVS1 1×10^{11} vp	Ad26COVS1 1×10^{11} vp
4 [c]	50	Ad26COVS1 1×10^{11} vp	Placebo
5 [c]	50	Placebo	Placebo
Total	**725**		

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 based on safety and immunogenicity results from the interim or primary analyses of Cohort 1a. After the primary analysis for safety of the selected single- or 2-dose primary regimen, Cohort 2 will include an evaluation of a single booster vaccination (see Table 2 for further details).
c. If only the higher dose level (1×10^{11} vp) in a 1- or 2-dose regimen meets the criteria for initiating an efficacy study based on results from Cohort 1, then the 5×10^{10} vp dose level will not be administered to participants in Cohort 3. In this case, 100 participants would be randomized to each of Groups 3 and 4, and 50 participants would be randomized to Group 5.

N = number of participants.

An internal DRC will be commissioned for this study to evaluate safety data over the course of the study and to review any events that meet a specific study pausing rule or any other safety issue that may arise (see Section 6.9, Study Vaccination Pausing Rules). Refer to Committees Structure in Section 10.2, Appendix 2, Regulatory, Ethical, and Study Oversight Considerations for details.

In Cohorts 1a and 3, participants will be enrolled in a staggered approach with safety evaluations in place before extending enrollment within the cohort and progressing from one cohort to the next (Figure 4). A diagram of the study design is provided in Section 1.2, Schema.

Cohort 1 (Adults Aged ≥18 to ≤55 Years)

The first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) in Cohort 1a, enrolled at the same study site, to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. In Cohort 1a, as for each cohort, participants will be closely observed for a minimum of 30 minutes post-vaccination for the development of acute reactions. A telephone call will be made to each of these 5 sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data, which will include solicited and unsolicited AEs and SAEs. The collected data will be reviewed in a blinded manner by the Principal Investigator (PI) and the sponsor's Study Responsible Physician (SRP). Randomization and vaccination of additional participants will be halted until the review is completed. In the absence of clinically significant findings, an additional 10 participants will be enrolled at the same study site as the 5 sentinel participants, randomly assigned to 1 of the 5 vaccination groups to have an overall 1:1:1:1:1 randomization ratio (ie, a total of 15 participants including the 5 sentinels, with 3 participants in each vaccination group), and administered the first vaccination.

The DRC will review the blinded 7-day safety data (ie, from Day 1 to Day 8) following administration of the first vaccination to the first 15 participants. Further randomization and vaccination of participants will be suspended until the DRC review is completed. Safety data for review will include solicited and unsolicited AEs and SAEs. In the absence of safety concerns, enrollment and vaccination of the remaining participants in Cohort 1a will continue and the enrollment and vaccination of participants in Cohort 1b will begin. The first 15 participants in Cohort 1a will progress to the second vaccination on Day 57. The second vaccination will be administered to the 5 sentinel participants first. The PI and SRP will also review blinded safety data from these participants following the second vaccination but randomization and vaccination of participants will not be halted during this review.

There will be 2 interim analyses of the data in Cohort 1a following the first study vaccination: interim analysis 1 examining safety data 28 days after the first study vaccination, and immunogenicity data 14 days after the first study vaccination if available based on operational considerations, and interim analysis 2 analyzing immunogenicity data 28 days after the first study vaccination (see Section 9.5, Planned Analysis).

There will also be 2 primary analyses in Cohort 1a following the second study vaccination: primary analysis 1 examining safety data at 28 days after the second study vaccination, and immunogenicity data 14 days after the second study vaccination if available based on operational considerations, and primary analysis 2 examining immunogenicity data 28 days after the second study vaccination.

Prespecified criteria may be used in the interim analyses and primary analyses of Cohort 1a to help guide selection of the optimal dose level and regimen, which will be used for Cohort 2. These criteria will be described in the Statistical Analysis Plan.

Cohort 2 (Adults Aged ≥18 to ≤55 Years)

When an optimal dose level and regimen are selected based on data from Cohort 1a, vaccination of participants in Cohort 2 will be initiated with this dose level and regimen. The Th1/Th2 response will be examined before vaccination of any participant in Cohort 2. A total of 150 participants will receive the selected Ad26COVS1 regimen and 50 participants will receive a placebo. No staggered enrollment will be performed for Cohort 2; however, the DRC will evaluate safety data from Cohort 2 over the course of the study. This safety cohort will contribute to the safety database prior to initiation of larger studies.

Even if a single-dose regimen is shown to induce an acceptable immune response in an interim analysis of Cohort 1a, it may still be decided that participants in Cohort 2 will receive a second dose of Ad26COVS1 if results from the primary analyses after the second study vaccination in Cohort 1a would support this regimen.

Combined safety results through 28 days after completion of the regimen in Cohorts 1a and 2 will be used to demonstrate the safety required to initiate larger scale studies with the vaccine. Data obtained after a single booster vaccination will be used to evaluate the effect of a booster vaccination at different time points and the duration of immune response (see below for further details).

Cohort 3 (Adults Aged ≥65 Years)

Upon confirmation of an acceptable safety and immunogenicity profile (including Th1/Th2 response) of Ad26COVS1 from the interim or primary analyses of Cohort 1a (see Section 9.5, Planned Analysis), the safety and immunogenicity of Ad26COVS1 in adults aged ≥65 years will be assessed in Cohort 3.

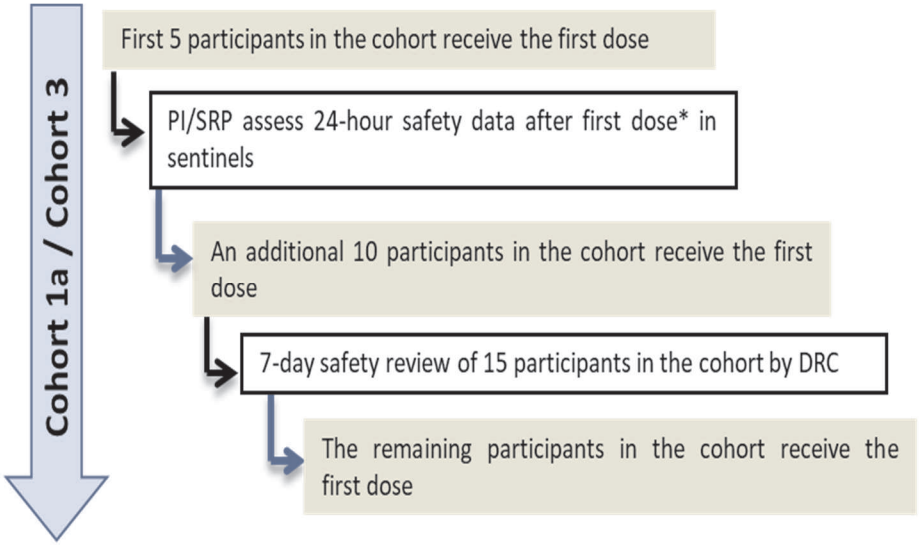
In Cohort 3, the first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. Safety evaluations and staggered enrollment of participants in Cohort 3, including DRC review of blinded 7-day safety data following administration of the first vaccination to the first 15 participants, will proceed in the same manner as that described for Cohort 1a and as detailed in Figure 4.

The dose level and regimen planned to be evaluated in Cohort 3 may be adjusted based on results from Cohort 1a. If only the higher dose level in a 1- or 2-dose regimen is selected from Cohort 1a, then the lower dose level will not be administered to participants in Cohort 3. In this case, 2 sentinel participants would be randomized to each of Groups 3 and 4, and 1 sentinel participant would be randomized to Group 5. In the absence of clinically significant findings from review of data from sentinel participants, an additional 10 participants would be randomized to 1 of the 3 vaccination groups to have an overall 2:2:1 randomization ratio (6 participants in each of Groups 3 and 4, and 3 participants in Group 5). In the absence of safety concerns from DRC review of 7-day safety data following administration of the first vaccination to the first 15 participants, enrollment and vaccination of participants would continue to have 100 participants randomized to each of Groups 3 and 4, and 50 participants randomized to Group 5 (see Table 1).

Based on the study design, participants in Cohort 3 will receive a second study vaccination, if applicable, only after the analysis of safety data from the primary analyses of Cohort 1.

Although it is anticipated that the initial efficacy study will be conducted in adults aged ≥18 to ≤55 years, it is important to establish safety and a regimen capable of inducing appropriate immunity for this candidate vaccine in elderly adults aged ≥65 years, as this group displays the highest incidence of morbidity and mortality in the current pandemic caused by SARS-CoV-2.

Figure 4: Participant Enrollment and First Dose Safety Strategy in Cohorts 1a and 3



DRC = Data Review Committee; PI = principal investigator; SRP = study responsible physician
*Sentinel participants will be contacted by telephone on Day 2 to collect safety information.

Single Booster Vaccination in Cohort 2

To gain preliminary insight into the safety and immunogenicity of a single booster vaccination, designated participants in Cohort 2 who received Ad26COVS1 for the single- or 2-dose primary regimen will receive a single booster vaccination of Ad26COVS1 at 6 months (Group 1a), 12 months (Group 1b), or 24 months (Group 1c) after completion of the primary regimen, and will receive placebo at other applicable time points. As a control, a subgroup of participants (Group 1d) who received Ad26COVS1 for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen. In addition, participants who received placebo for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen (Group 2) (Table 2). The same Ad26COVS1 dose level that was administered in the primary regimen will be used for the booster vaccination.

Table 2: Cohort 2 Vaccination Schedule – Primary Regimen and Single Booster Vaccination

		Primary Regimen		Booster Vaccination		
Group	N	Day 1 [a] (Vac 1)	Day 57 [a] (Vac 2)	+6 months [b]	+12 months [b]	+24 months [b]
1a	40	Ad26COVS1	Ad26COVS1	Ad26COVS1	Placebo	Placebo
1b	40	Ad26COVS1	Ad26COVS1	Placebo	Ad26COVS1	Placebo
1c	40	Ad26COVS1	Ad26COVS1	Placebo	Placebo	Ad26COVS1
1d	30	Ad26COVS1	Ad26COVS1	Placebo	Placebo	Placebo
2	50	Placebo	Placebo	Placebo	Placebo	Placebo
Total	**200**					

a. Study vaccine will be administered as a single-dose (Day 1) or 2-dose (Day 1 and Day 57) primary regimen based on safety and immunogenicity results from the interim or primary analyses of Cohort 1a.

b. Study vaccine (Ad26COVS1 or a placebo) will be administered at 6 months, 12 months, and 24 months after completion of the single-dose or 2-dose primary regimen. The same Ad26COVS1 dose level will be used as selected for the primary regimen.

N = number of participants; vac = vaccination.

Study Duration

For Cohorts 1 and 3, the study duration from screening until the last follow-up visit will be approximately 13 months per participant. For these cohorts, the study consists of a screening period of up to 28 days, vaccinations on Day 1 and Day 57, and follow-up visits up to 12 months after the first vaccination (Target Visit Day 366±21 days).

For Cohort 2, if a single-dose primary regimen is selected, the study duration from screening until the last follow-up visit will be approximately 30 months per participant. In this case, the study would consist of a screening period of up to 28 days, vaccination on Day 1, a single booster vaccination at 6 months, 12 months, or 24 months after completion of the primary regimen on Day 1, and follow-up visits up to 30 months after completion of the primary regimen on Day 1 (Target Visit Day 913±21 days).

If a 2-dose primary regimen is selected for Cohort 2, the study duration from screening until the last follow-up visit will be approximately 32 months per participant. In this case, the study would consist of a screening period of up to 28 days, vaccinations on Day 1 and Day 57, a single booster vaccination at 6 months, 12 months, or 24 months after completion of the primary regimen on Day 57, and follow-up visits up to 30 months after completion of the primary regimen on Day 57 (Target Visit Day 969±21 days).

For each cohort, if a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted.

Enrollment of Seropositive Participants

For all participants, a rapid serological test, if available, will be performed at screening to detect SARS-CoV-2-specific antibodies. Should a suitable rapid serological test not be available, over-enrollment will be permitted to ensure that a minimum number of seronegatives are enrolled in the study.

In Cohort 1a and 3, the first 15 participants to be randomized will be seronegative participants. After DRC review of 7-day of blinded safety data, a maximum of 25 seropositive participants will be enrolled among the remaining participants in Cohorts 1a and 3. No seropositive participants will be enrolled in Cohort 1b. A maximum of 25 seropositive participants will be enrolled in Cohort 2.

Enrollment of seropositives in the present study will allow an evaluation of vaccine safety in this group. The number of seropositive participants is limited so that it does not affect the sample size of seronegative participants.

Study Procedures

For each cohort, safety will be assessed by collection of solicited local (at injection site) and systemic AEs, unsolicited AEs, and SAEs. Other safety assessments include vital signs measurements (heart rate, supine systolic and diastolic blood pressure, respiratory rate, body temperature) and physical examinations at the time points indicated in Section 1.3, Schedule of Activities.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. Any solicited local or systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period. In addition, participants will record solicited events signs and symptoms in a diary for 7 days post-vaccination.

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. If a participant experiences COVID-19-like symptoms (eg, cough, feverishness, dyspnea, gastrointestinal symptoms, anosmia), the following should take place:

- Participants should contact the study site at the time of symptom onset.
- Participants should collect a nasal swab at home (using available material for home swabs) as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms, and store it appropriately. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected by the participant. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab or at the study site if appropriate procedures are in place. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by rapid molecular testing using the nasal swab sample.
- Participants should complete the COVID-19 Signs and Symptoms Instrument (CSSI) and Global Impression of Severity, and record their highest body temperature daily, starting on

the first day they experience symptoms, and the Global Impression of Change starting from the day after they first experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.

Further details are provided in Section 8.1.1, Procedures in Case of COVID-19-like Signs and Symptoms.

4.2. Scientific Rationale for Study Design

Vector Selection

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

Dose Selection

The rationale behind the selection of the doses is described in Section 4.3, Justification for Dose.

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 clinical and immunological 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 interactive web response system (IWRS).

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 benefit from participation in the study, except for compensation for the time and inconveniences that may arise from participation in the study. See Section 2.3, Benefit-Risk

Assessment for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

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,[40,41] as well as the Belgian Red Cross guidelines of 450-470 mL up to 4 times a year with at least 2 months between each donation.[6]

4.3. Justification for Dose

The regimens and dose selection in this study are aimed at providing information on safety and immunogenicity of a single-dose or 2-dose schedule of the Ad26COVS1 vaccine. The regimen selected is based on previous preclinical and clinical data from other Ad26-based vaccines.

Overall, Ad26 vaccine candidates have an acceptable safety profile. The safety data from studies with other Ad26-based vaccines are summarized in Section 2.3.1, Risks Related to Study Participation. Safety data from studies with other Ad26-based vaccines expressing different antigens are supportive of dosing Ad26COVS1 at $5x10^{10}$ vp and $1x10^{11}$ vp in the current study.[1]

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the 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

For Cohorts 1 and 3, a participant will be considered to have completed the study if he or she has completed assessments at Day 366; participants who prematurely discontinue study vaccine for any reason before completion of Day 366 will not be considered to have completed the study.

For Cohort 2, a participant will be considered to have completed the study if he or she has completed assessments at 6 months after completion of the last booster vaccination for any group. Participants who prematurely discontinue study vaccine for any reason before that time will not be considered to have completed the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before the first study vaccination.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about the inclusion or exclusion criteria below, the investigator must consult

with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

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

1. Participant must sign an ICF 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. Applicable to Cohorts 1 and 2 only: Participant is male or female and 18 to 55 years of age, inclusive, on the day of signing the ICF.

   Applicable to Cohort 3 only: Participant is male or female and 65 years of age or older on the day of signing the ICF.
4. Applicable to Cohorts 1 and 3 only: Participant must have a body mass index (BMI) <40 kg/m^2.
5. Applicable to Cohorts 1 and 2 only: Participant must be healthy as confirmed by medical history, physical examination, and vital signs performed at screening.

   Applicable to Cohort 3 only: In the investigator's clinical judgment, participant must be either in good or stable health. Participants may have underlying illnesses such as hypertension, type 2 diabetes mellitus, hyperlipoproteinemia, or hypothyroidism, as long as their symptoms and signs are medically controlled. If they 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 physical examination, medical history and vital signs[a].
6. Applicable to Cohorts 1 and 2 only: Contraceptive (birth control) use by women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

   Before randomization, participants who were born female must be either (as defined in Section 10.4, Appendix 4, Contraceptive Guidance and Collection of Pregnancy Information):

   a. Not of childbearing potential
   b. Of childbearing potential and practicing a highly effective method of contraception and agrees to remain on such a method of contraception from signing the informed consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first vaccination. Highly effective methods for this study include:
      1) hormonal contraception;

[a] Participants can be enrolled with Grade 1 or Grade 2 values for vital signs measurements.

2) intrauterine device (IUD);

3) intrauterine hormone-releasing system (IUS);

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 signing the informed consent until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Applicable to Cohort 3 only: Before randomization, a woman must be (as defined in Section 10.4, Appendix 4, Contraceptive Guidance and Collection of Pregnancy Information):

a. postmenopausal (postmenopausal state is defined as no menses for 12 months without an alternative medical cause) or permanently sterile; and

b. not intending to conceive by any methods.

7. All female 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 immediately prior to each study vaccine administration.

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

9. Participant must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

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 first dose of study vaccine; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.
2. Participant history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
3. Participant has a known 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).
4. Participant has abnormal function of the immune system resulting from:

a. Clinical conditions (eg, autoimmune disease or immunodeficiency) expected to have an impact on the immune response elicited by the study vaccine. Participants with clinical conditions stable under treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis, and diabetes types 1 and 2) may be enrolled at the discretion of the investigator.

b. Chronic (>10 days) or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study.
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.

5. Participant has a history of acute polyneuropathy (eg. Guillain-Barré syndrome).
6. Participant has a history of chronic urticaria (recurrent hives), eczema or adult atopic dermatitis.
7. Participant received treatment with immunoglobulins (Ig) in the 2 months or blood products in the 4 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.
8. Participant received or plans to receive:

   a. Licensed live attenuated vaccines - within 28 days before or after planned administration of the first or second study vaccination

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

9. Participant received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study. Note: Participation in an observational clinical study is allowed at the investigator's discretion; please notify the sponsor (or medical monitor) of this decision.
10. Participant is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study vaccine.
11. 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.
12. Participant had major surgery, per the investigator's judgment, within 12 weeks before vaccination, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to participate in the study or within 6 months after the last dose of study vaccine administration.
13. Participant has a contraindication to IM injections and blood draws eg, bleeding disorders.
14. Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.

15. Participant has chronic active hepatitis B or hepatitis C infection per medical history.
16. Participant has HIV infection per medical history.
17. 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.
18. Participant cannot communicate reliably with the investigator.
19. 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.
20. Participant previously received a coronavirus vaccine.
21. Participant has a positive diagnostic test result for SARS-CoV-2 infection at screening.
22. Based on a serological test at screening, if available:
    Applicable to Cohorts 1a, 2, and 3 only: after a limited number of seropositive participants have been enrolled, further seropositive participants will be excluded (see Section 4.1, Overall Design).
    Applicable to Cohort 1b only: seropositive participants will be excluded.

NOTE: Investigators should ensure that all study enrollment criteria have been met prior to the first dose. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of 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. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2, Appendix 2, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Prestudy and Concomitant Therapy 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.

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. 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.

An individual who does not meet the criteria for participation in this study (screen failure) may be rescreened on one occasion only. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart 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.

If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for one of the subsequent vaccinations, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in Section 8, Study Assessments and Procedures).

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

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1. Study Vaccinations Administered

Ad26COVS1 will be supplied at a concentration of $1x10^{11}$ vp/mL in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer will be supplied as 15 mM citrate, 5% (w/w) hydroxypropyl-β-cyclodextrin, 0.4% (w/w) ethanol, 0.03% (w/w) polysorbate 80, 75 mM NaCl, pH 6.2 and placebo is 0.9% NaCl.

For blinding purposes, the same volume will be administered to all participants in a cohort.

Study vaccine will be administered by IM injection into the deltoid muscle, preferably of the non-dominant arm:

Cohorts 1 and 3:

A volume of 1 mL will be administered to all participants.

- Ad26COVS1:
  - $5x10^{10}$ vp: 0.75 mL of formulation buffer is withdrawn from one vial and added to a vial containing 0.75 mL $1×10^{11}$ vp/mL, providing $5x10^{10}$ vp/mL in a vial with an extractable volume of more than 1 mL. Then 1 mL will be withdrawn from this vial.

  - $1x10^{11}$ vp: 2 single-use vials (0.5 mL will be withdrawn from 1 vial and added to a second vial, which will then have an extractable volume of more than 1 mL. Then, 1 mL will be withdrawn from the second vial).

- Placebo: 0.9% NaCl solution: 1 mL

Cohort 2:

If the selected dose level of Ad26COVS1 is $1x10^{11}$ vp:

A volume of 1 mL will be administered to all participants.

- Ad26COVS1: $1x10^{11}$ vp: 2 single-use vials (0.5 mL will be withdrawn from 1 vial and added to a second vial, which will then have an extractable volume of more than 1 mL. Then, 1 mL will be withdrawn from the second vial)
- Placebo: 0.9% NaCl solution: 1 mL

If the selected dose level Ad26COVS1 is $5x10^{10}$ vp:

A volume of 0.5 mL will be administered to all participants.

- Ad26COVS1: 0.5 mL is withdrawn from a vial containing $1x10^{11}$ vp/mL
- Placebo: 0.9% NaCl solution: 0.5 mL

Study vaccine administration must be captured in the source documents and the electronic case report form (eCRF).

Ad26COVS1 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

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 site investigational product and procedures manual (SIPPM) and the Investigational Product Preparation Instructions (IPPI) for additional guidance on study vaccine preparation, handling, and storage.

An unblinded pharmacist or other qualified individual who will have no other study function will prepare the appropriate vial and syringe, labeled with the participant's identification number, and provide the syringe to the blinded vaccine administrator 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 study 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 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 supplied 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 vaccines are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Vaccine Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Within each cohort, participants will be randomly assigned to 1 of the vaccine groups 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. For Cohorts 1 and 3, randomization will be stratified by study site and seropositivity status at screening. For Cohort 2, randomization will be stratified study site, seropositivity status at screening, and age group (≥18 to ≤40 years and >40 to ≤55 years). For Cohort 2, participants will be randomized to different booster vaccination schedules.

The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit 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

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

Under normal circumstances, the blind should not be broken until the database is finalized. 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 IWRS, and in the source document.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis. Refer to Section 9.5, Planned Analysis, for details of the analyses.

If randomized participants are withdrawn from vaccination before the first dose of study vaccine is administered, additional participants may be recruited to replace these participants at the discretion of the sponsor. Any replacement participant will be assigned to the same group as the original (discontinued) participant. If randomized participants are withdrawn after the first dose of study vaccine is administered, they will not be replaced.

6.4. Study Vaccine Compliance

Study vaccines will be administered IM by blinded qualified study site personnel at the study site. Details of each administration will be recorded in the CRF (including date and time of injection

and deltoid used for injection). For blinding procedures, see Section 6.3, Measures to Minimize Bias: Randomization and Blinding.

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

There will be no study vaccination after the end of the study.

6.7. Treatment of Overdose

For this study, any dose of Ad26COVS1 greater than the assigned dose will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs: (ie, the participant will remain at the study site for at least 1 hour and will be closely monitored for allergic or other reaction by study staff. A follow-up telephone call 12 hours and 24 hours post-dose will be made).
- Document the quantity of the excess dose in the CRF.
- Report as a special reporting situation.

6.8. Prestudy and Concomitant Therapy

Prestudy specific therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations administered up to 30 days before first dose of study vaccine must be recorded at screening.

Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outline in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is not allowed. Participants may not receive an investigational drug or use an invasive investigational medical device within 30 days or receive an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine.

Vaccination with licensed live attenuated vaccines within 28 days of a study vaccination (ie, before or after) is prohibited. Other licensed (not live) vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) 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 is prohibited during the study and within 6 months before the planned administration of the first dose of 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, Exclusion Criteria 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 medication will not be included in the immunogenicity analyses.

6.9. Study Vaccination Pausing Rules

For Cohorts 1a and 3, randomization and vaccination of participants will be suspended during review of the 24-hour data following the first administration of study vaccine to 5 sentinel participants and during review of the 7-day safety data after the first 15 participants have received the first vaccination (see Section 4.1, Overall Design).

For each cohort, the PI and the SRP will monitor safety in a blinded manner, including the study vaccination pausing rules. If a study vaccination is considered to raise significant safety concerns (and a specific set of pausing criteria have been met), further vaccination of participants will be paused. The concerned data will be reviewed by the DRC, after which the DRC will recommend whether the pause can be lifted or not, or whether other steps are needed.

The DRC will review blinded data first, but has the right to request the randomization codes and review unblinded data if deemed necessary. The DRC will make recommendations regarding the continuation of the study to the sponsor study team. The sponsor study team will communicate conclusions regarding study continuation to the investigator, the IEC/IRB and applicable health authorities as appropriate.

After the first DRC meeting triggered by the occurrence of a given pausing rule, the DRC will convene thereafter for each additional participant meeting that pausing rule.

The occurrence of any of the following events will lead to a pause in further study vaccination. Laboratory abnormalities noted below refer to cases where the study-site personnel perform laboratory safety testing for investigation of an AE. This list is only applicable for concerned AEs that occur up to 4 weeks after each vaccination and to concerned SAEs.

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

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

   Note: All cases of death will be sent for DRC information. Upon their review, the DRC may then decide whether a study pause is required.

2. One or more participants experience an SAE or a Grade 4 (solicited or unsolicited) AE or a persistent (upon repeat testing) Grade 4 laboratory abnormality that is determined to be related to study vaccine; OR
3. One or more participants experience anaphylaxis or generalized urticaria within 24 hours of vaccination, clearly not attributable to other causes than vaccination with study vaccine; OR
4. Three or more participants experience a Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor), that is determined to be related to study vaccine; OR
5. Three or more participants experience a persistent (upon repeat testing) Grade 3 laboratory abnormality related to the same laboratory parameter and considered related to study vaccine; OR
6. Three or more participants experience a Grade 3 solicited AE of the same type, determined to be related to study vaccine, and persisting as Grade 3 for longer than 3 consecutive days[a].

For number 2 and number 5: to assess abnormal laboratory values, the test must be repeated at least once, within 48 hours of the site becoming aware of the abnormal value.

For number 4, number 5, and number 6: after each DRC review of similar AEs, the Committee will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

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 SAE form to Global Medical Safety Operations, if applicable), immediately and no later than 24 hours after becoming aware of any related AE of Grade 3 or above AND update the CRF with relevant information on the same day the AE information is collected. A thorough analysis of all Grade 3 (or above) cases will be carried out by the sponsor's medical monitor or designee, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted. All sites will be notified immediately in case of a study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of DRC members and coordination of a DRC meeting in case of a study pause.

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 DRC review for any

[a] The day of occurrence of the AE is counted as Day 1.

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 judgment of the DRC, participant safety may be threatened.

Resumption of vaccinations will start only upon receipt of written recommendations by the DRC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. These communications from the DRC 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

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

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

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic (>10 days) or recurrent use of systemic corticosteroids and administration of antineoplastic and immunomodulating agents or radiotherapy
- Withdrawal of consent
- Participant has a positive test result for SARS-CoV-2 infection during the study (see Section 8.1.1).

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 CRF 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 10.2, Appendix 2, Regulatory, Ethical, and Study Oversight Considerations). 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

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 Schedule of Activities summarizes the frequency and timing of safety, reactogenicity, and immunogenicity measurements applicable to each cohort in this study. See Section 1.3 for details.

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. Actual dates and times of assessments will be recorded in the source document and in the CRF.

Participants will be provided a thermometer (to measure body temperature), ruler (to measure local injection site reactions), and participant diary to record body temperature and solicited local (at injection site) and systemic signs and symptoms. The 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 diary will be reviewed by the study personnel at visits indicated in the Section 1.3, Schedule of Activities. If the diary review is missed, the diary will be reviewed during the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be completed.

Participants will also be provided with a booklet (to answer a daily signs and symptoms surveillance question, and including the CSSI and global impression questions) and a kit to collect nasal swabs if they experience COVID-19-like symptoms during the study (see Section 8.1.1, Procedures in Case of COVID-19-like Signs and Symptoms).

For each participant, the maximum amount of blood drawn in this study will not exceed approximately 737 mL for Cohorts 1a or 3, 997 mL for Cohort 1b, and 710 mL for Cohort 2. Refer to Section 1.3, Schedule of Activities for the total blood volume (serum and, as applicable, PBMC and whole blood samples) to be collected at each visit and over the complete course of the study for each cohort. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Study visits, other than screening and visits at which study vaccination is scheduled, may take place at the participant's home if there are travel restrictions in case of an ongoing pandemic.

Visit Windows

Visit windows that will be allowed are summarized in Table 3 and Table 4. 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. If a participant misses a vaccination, the post-vaccination visits will be calculated from the imputative vaccination date according to protocol.

Table 3: Visit Windows Cohorts 1 and 3

Visit	Target Visit Day	Allowed Window	Primary Purpose
4 [a]	8	±2 days	7 days post-vaccination 1 safety visit
5	15	±3 days	14 days post-vaccination 1 safety and immunogenicity visit
6	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
7	57	-3/+7 days	Vaccination 2
9 [a]	64 [b]	±2 days	7 days post-vaccination 2 safety visit
10	71 [b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
11	85 [b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
12	239 [b]	±21 days	6 months post-vaccination 2 safety and immunogenicity visit
13	366	±21 days	12 months post-vaccination 1 safety and immunogenicity visit

a. If a participant comes in early for Visit 4 or 9 ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will then be returned by the participant at the next visit. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

b. The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

Table 4: Visit Windows Cohort 2 (Single-dose Primary Regimen)

Visit	Target Visit Day	Allowed Window	Primary Purpose
3	29	±3 days	Safety and immunogenicity visit 28 days after primary regimen
4	57	-3/+7 days	Safety and immunogenicity visit 56 days after primary regimen
5	183	±21 days	Safety and immunogenicity visit / single booster vaccination 6 months after primary regimen [b]
6	211 [a]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
7	366	±21 days	Safety and immunogenicity visit / single booster vaccination 12 months after primary regimen [b]
8	394 [a]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
9	731	±21 days	Safety and immunogenicity visit / single booster vaccination 24 months after primary regimen [b]
10	759 [a]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
11	913 [a]	±21 days	Safety and immunogenicity visit 6 months post-booster vaccination

a. The timings of visits after a booster vaccination will be determined relative to the actual day of that vaccination.

b. Participants designated to receive a single booster vaccination will receive Ad26COVS1 at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other indicated time points. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

Table 5: Visit Windows Cohort 2 (Two-dose Primary Regimen)

Visit	Target Visit Day	Allowed Window	Primary Purpose
3	29	±3 days	Safety and immunogenicity visit 28 days post-vaccination 1
4	57	-3/+7 days	Vaccination 2
5	85 [a]	±3 days	Safety and immunogenicity visit 28 after primary regimen
6	239 [a]	±21 days	Safety and immunogenicity visit / single booster vaccination 6 months after primary regimen [b]
7	267 [a]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
8	422 [a]	±21 days	Safety and immunogenicity visit / single booster vaccination 12 months after primary regimen [b]
9	450 [a]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
10	787 [a]	±21 days	Safety and immunogenicity visit / single booster vaccination 24 months after completion of primary regimen [b]
11	815 [a]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
12	969 [a]	±21 days	Safety and immunogenicity visit 6 months post-booster vaccination

a. The timings of visits after the second vaccination or a booster vaccination will be determined relative to the actual day of that vaccination.
b. Participants designated to receive a single booster vaccination will receive Ad26COVS1 at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other indicated time points. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

Screening

Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 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 4 weeks prior to first 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 molecular test for the presence of SARS-CoV-2 infection must be done within 24 hours before vaccination. The study-specific ICF date will be entered into the CRF. 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 CRF or laboratory requisition form. Refer to Section 1.3, Schedule 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 Ad26COVS1
- Thermometer
- Ruler (to measure diameter of any erythema and swelling)
- Pharmacy manual/SIPPM
- IWRS Manual
- Sample ICF
- Laboratory manual
- Participant diaries
- Nasal swab kits
- Participant instructions and booklet: COVID-19-like signs and symptoms daily surveillance, nasal swab instructions, and CSSI and global impression questions (for daily completion, if symptomatic)
- Contact information page(s)

8.1. Immunogenicity Assessments

Venous blood samples will be collected for assessment of humoral or cellular immune responses. Sample volumes and time points are detailed in the Schedule of Activities for Cohort 1a (Section 1.3.1), Cohort 1b (Section 1.3.2), Cohort 2 (Section 1.3.3), and Cohort 3 (Section 1.3.3.2.2).

If the participant is unable to complete the study without withdrawing consent, immunogenicity samples will be taken at the early exit visit, but only if the early exit visit is at least 10 days after the previous immunology blood draw.

Humoral and cellular immunogenicity assays may include, but are not limited to, the assays summarized in Table 6 and Table 7, respectively.

Table 6: Summary of Humoral Immunogenicity Assays

Assay	Purpose
Secondary endpoints	
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 (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
Exploratory endpoints	
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other strain), as measured by an alternative neutralization assay (different from the VNA used for the secondary endpoint)
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein, if such an assay can be developed
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model

ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay

Table 7: Summary of Cellular Immunogenicity Assays

Assay	Purpose
Secondary endpoints	
Flow cytometry (ICS) Or ELISpot	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by ICS including $CD4^+$/$CD8^+$, IFNγ, IL-2,TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers Or IFNγ and IL-4 responses to SARS-CoV-2 S protein, and/or other SARS-CoV-2 protein peptides by PBMCs, based on dual or single ELISpot
Exploratory endpoints	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling and/or analysis of protein translates, in cells or whole blood stimulated with SARS-CoV-2 S protein, other SARS-CoV-2 protein peptides, or in unstimulated cells or whole blood (ex vivo)
Cytokine profiling (ELISA or multiplexed arrays)	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in whole blood stimulated with SARS-CoV-2 S protein, other SARS-CoV-2 protein peptides, or in unstimulated cells or whole blood by ELISA or multiplexed arrays and confirmation by functional in vitro assays
T and B cell phenotyping	Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube isolated PBMCs)

ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot (assay); ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; S = spike; SARS-CoV 2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha

8.1.1. Procedures in Case 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 Schedule of Activities in Section 1.3.5.

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. Participants will also be contacted regularly by study site personnel during the study to remind them to complete the CSSI and global impression questions in the event of any signs and symptoms and to contact the site at the time of symptom onset.

For each cohort, if participants experience COVID-19-like symptoms (eg, cough, feverishness, dyspnea, gastrointestinal symptoms, anosmia), the following should take place:

- Participants should contact the study site at the time of symptom onset.
- Participants should collect a nasal swab at home (using available material for home swabs) as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms, and store it appropriately. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected by the participant. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab or at the study site if appropriate procedures are in place. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by rapid molecular testing

using the nasal swab sample. Leftover nasal swab samples will be stored and might be used for central laboratory confirmation and/or quantification of SARS-CoV-2 and for detection of other respiratory pathogens.

- Participants should complete the CSSI and Global Impression of Severity, and record their highest body temperature daily, starting on the first day they experience symptoms, and the Global Impression of Change starting from the day after they first experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.

If a participant has a positive test result for SARS-CoV 2 infection, the participant may be requested to remain at home and not visit the study site. If necessary, study site personnel will visit the participant at home. 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. The participant will not receive further study vaccinations but should remain on study for follow-up with assessments of safety and immunogenicity.

If a participant has a positive test result for influenza infection, study visits will continue per the Schedule of Activities.

8.1.2. Efficacy

As an exploratory objective, a preliminary analysis of vaccine efficacy in the prevention of molecularly confirmed COVID-19 will be performed. Identification and molecular confirmation of SARS-CoV-2 infection will be performed as described in Section 8.1.1, Procedures in Case of COVID 19-like Signs and Symptoms.

As an additional exploratory objective, a preliminary analysis of vaccine efficacy in the prevention of asymptomatic SARS-CoV-2 infection will be performed. A non-S protein ELISA (eg, SARS-CoV-2 N ELISA), if such an assay can be developed, will be performed to identify cases of asymptomatic infection.

8.2. Safety Assessments

Details regarding the DRC are provided in Committees Structure in Section 10.2, Appendix 2, Regulatory, Ethical, and Study Oversight Considerations.

AEs will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.3, Appendix 3, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event 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 Schedule of Activities.

8.2.1. Physical Examinations

A full physical examination, including height and body weight, will be carried out at screening. To obtain the actual body weight, participants must be weighed lightly clothed. The height should be measured without footwear.

At all other visits, an abbreviated, symptom-directed examination might be performed by the investigator based on any clinically relevant issues or symptoms, and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or designated medically trained clinician. 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

Body temperature (oral route preferred, or in accordance with the local standard of care), pulse/heart rate, respiratory rate, and blood pressure will be assessed. Confirmatory vital signs measurement can be performed if inconsistent with a prior measurement.

Participants will utilize a diary to record body temperature measurements post-vaccination.

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

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

8.2.3. Pregnancy Testing

For Cohorts 1 and 2 only, a urine pregnancy test for women of childbearing potential will be performed at screening and before each vaccination.

Additional pregnancy tests may be performed, 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.

8.2.4. Clinical Laboratory Assessments

A hemoglobin laboratory test will be performed at a local laboratory on pre-vaccination blood samples on Day 1, which will allow the investigator to judge the appropriateness of further blood sampling for the participant after the first vaccination.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, 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) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.3, Appendix 3, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

AEs and special reporting situations, whether serious or non-serious, 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 ICF and moment of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Solicited AEs, collected through a diary, will be recorded for each vaccination from the time of vaccination until 7 days post-vaccination.

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first 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.

All AEs will be followed until resolution or until clinically stable.

Serious Adverse Events

All SAEs, as well as PQC, 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 within 30 days after the last dose of study vaccine, 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.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event 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 a 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 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 the injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their diary.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events.

In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination. All participants will be provided with a diary and instructions on how to complete the diary (see Overview in Section 8, Study Assessments and Procedures). Diary information will be transferred to the sponsor. After review and verbal discussion of the initial diary entries with the participant, the investigator will complete his/her own assessment in the relevant sections of the eCRF. Once a solicited sign or symptom from a 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 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.[21,29]

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 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 one measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[34]

Participants will also be instructed on how to note signs and symptoms in the 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, and myalgia.

Unsolicited Adverse Events

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

8.3.3. Follow-up of 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, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs, including pregnancy, will be followed by the investigator as specified in Section 10.3, Appendix 3, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 Independent Ethics Committee/Institutional Review Board (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 female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study vaccination.

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

8.4. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

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 Statistical Analysis Plan.

9.1. Statistical Hypotheses

No formal statistical hypothesis for safety or immunogenicity will be tested.

9.2. Sample Size Determination

The number of participants chosen for this study will provide a preliminary safety and immunogenicity assessment. Placebo recipients are included for blinding and safety purposes and will provide additional control specimens for immunogenicity assays.

While mild-to-moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. When 50 and 150 participants are vaccinated, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 5.8% and <2.0% respectively. Table 8 provides the probabilities of observing at least one AE at given true AE rates.

Table 8: Probability of Observing at Least One Adverse Event Given a True Adverse Event Incidence

	Probability of Observing at Least One Adverse Event	
True Adverse Event Incidence	**N=50**	**N=150**
1%	39%	78%
2.5%	72%	98%
5%	92%	>99%
10%	>99%	>99%
20%	>99%	>99%

N: number of participants receiving study vaccine (Ad26COVS1 or a placebo).

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

FAS: The full analysis set will include all participants with at least one vaccine administration documented.

PPI: The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, samples

obtained after missed vaccinations or participants with natural infection occurring after screening (if applicable) will be excluded from the analysis set.

PPE: The per protocol efficacy population will include all randomized participants having received at least 1 vaccination for whom efficacy data concerning endpoint measures are available. All efficacy analyses will be done according to the as treated principle (ie, actually received vaccinations).

9.4. Statistical Analyses

The Statistical Analysis Plan will be finalized prior to interim DBL 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.

9.4.1. General Considerations

Analysis populations are defined in Section 9.3, Populations for Analysis Sets. Planned analyses are defined in Section 9.5, Planned Analysis.

For safety and immunogenicity analyses, results will be analyzed by vaccine group. In addition, safety and immunogenicity analyses will be repeated by vaccine group and participant seropositivity status at screening. Immunogenicity subanalyses will also be performed by BMI, ethnicity, and other factors as will be described in the Statistical Analysis Plan.

9.4.2. Primary Endpoints

Safety Endpoints

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group. In addition, for selected tables, tabulations pooled by vaccine dose will also be provided. All safety analyses will be made on the FAS.

Adverse Events

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 will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by vaccine group.

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

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The number and percentages of participants with at least one solicited local (at injection site) or systemic AE will be presented. The 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

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Physical examination findings will be summarized at baseline. A listing of the abnormalities will be made.

9.4.3. Secondary Endpoints

Immunogenicity Endpoints

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval, or median and interquartile range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters at all available time points. Graphical representations of immunologic parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

In addition, the ratio between neutralizing and binding antibodies as determined by S protein ELISA and VNA, respectively, will be calculated.

The immunogenicity analyses will be performed on the PPI population. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols).

9.4.4. Tertiary/Exploratory Endpoint(s)

Detailed statistical methodology for analysis of exploratory endpoints will be described in the Statistical Analysis Plan.

9.4.5. Other Analyses

Descriptive analysis will be performed for the results of the CSSI and global impression questions, and results of diagnostic tests for SARS-CoV-2 infection after screening. Further details will be provided in the Statistical Analysis Plan.

9.5. Planned Analysis

Interim and primary analyses for each cohort are presented in Figure 5.

Interim and Primary Analyses for Cohort 1a

A first interim analysis post-dose 1 for Cohort 1a is planned when all 250 participants have completed Day 29 (ie, 28 days after the first study vaccination) or discontinued earlier. This interim analysis will include safety data for all 250 participants through Day 29 and may include

immunogenicity data (VNA, ELISA and Th1/Th2 assay; ADCP assay, if available and feasible) for at least 25 seronegative participants (ie, participants who were seronegative at screening) per group through Day 15 (ie, 14 days after the first study vaccination)[a]. A second interim analysis for Cohort 1a will include immunogenicity data (VNA, ELISA, and Th1/Th2 assay) for at least 25 seronegative participants per group through Day 29. This will supplement the first interim analysis as the maximal immune response might occur later than Day 15 post-vaccination in naïve individuals. For logistical reasons, aspects of the first and second interim analyses may be combined.

The first primary analysis post-dose 2 for Cohort 1a will be performed when all 250 participants have completed Day 85 (ie, 28 days after the second study vaccination) or discontinued earlier. The primary analysis will include safety data for all participants through Day 85. It may also include immunogenicity data (all available data for seronegative participants for the VNA, ELISA, and Th1/Th2 assay, and for the ADCP assay, if available and feasible,) through Day 71 (ie, 14 days after the second study vaccination)[a]. A second primary analysis for Cohort 1a will include immunogenicity data through Day 85 (all available data for seronegative participants for the VNA, ELISA, and Th1/Th2 assay). For logistical reasons the first and second primary analyses may be combined.

Interim and Primary Analyses for Cohort 2

An interim safety analysis for Cohort 2 will be performed when 28 day safety data is collected for all 200 participants after the completion of the selected regimen. This safety analysis will be the basis for enrollment of adults aged ≥18 to ≤55 years in larger subsequent studies.

The primary analysis for Cohort 2 will include safety data for all 200 participants through 28 days after completion of the selected regimen. It will also include immunogenicity data (VNA and ELISA) for at least 25 seronegative participants in the Ad26COVS1 group and 10 seronegative participants in the placebo group.

Interim analyses of the data from each booster vaccination will be performed after the last participant receives their respective booster vaccination and will include safety and immunogenicity data up to 28 days after the vaccination.

Interim and Primary Analyses for Cohort 3

The analysis strategy for Cohort 3 is the same as for Cohort 1a.

A first interim analysis post-dose 1 for Cohort 3 is planned when all 250 participants have completed Day 29 (ie, 28 days after the first study vaccination) or discontinued earlier. This interim analysis will include safety data for all 250 participants through Day 29 and may include immunogenicity data (VNA, ELISA, and Th1/Th2 assay; ADCP assay, if available and feasible) for at least 25 seronegative participants per group through Day 15 (ie, 14 days after the

[a] May be performed based on operational availability of data.

first study vaccination)[a]. A second interim analysis for Cohort 3 will include immunogenicity data (VNA, ELISA, and Th1/Th2 assay) for at least 25 seronegative participants per group through Day 29. This will supplement the first interim analysis as the maximal immune response might occur later than Day 15 post-vaccination in naïve individuals. For logistical reasons the first and second interim analyses may be combined.

The first primary analysis post-dose 2 for Cohort 3 will be performed when all 250 participants have completed Day 85 (ie, 28 days after the second study vaccination) or discontinued earlier. The primary analysis will include safety data for all participants through Day 85. It may also include immunogenicity data (all available data for seronegative participants for the VNA, ELISA, and Th1/Th2 assay; ADCP assay, if available and feasible) through Day 71 (ie, 14 days after the second study vaccination)[a]. A second primary analysis for Cohort 3 will include immunogenicity data through Day 85 (all available data for seronegative participants for the VNA, ELISA, and Th1/Th2 assay). For logistical reasons the first and second primary analyses may be combined.

Final Analysis of the Study

The final analysis will be performed when the last participant from Cohorts 1a and 3 completes the final visit (Visit 13, 12 months after first study vaccination) or discontinues earlier. It will include any data for Cohorts 1a and 3 that were not available for the interim and primary analyses and all data that are available for Cohorts 1b and 2 (including any data after booster vaccinations). It will also include data from participants in each cohort who were seropositive for SARS-CoV-2-specific antibodies at screening.

End-of-study Analysis

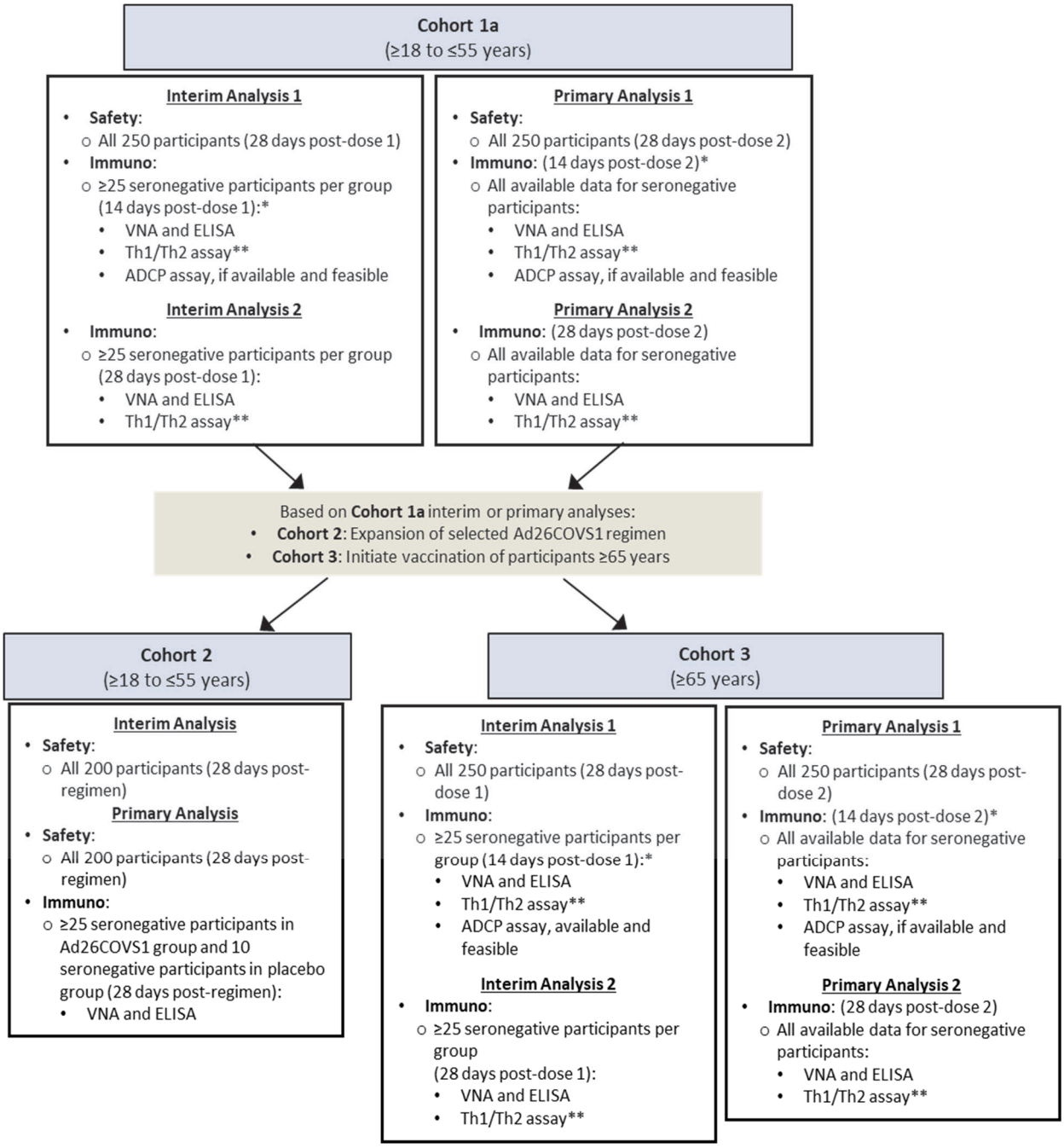
The end-of-study analysis will be performed when all included participants have completed the last visit or last booster vaccination follow-up visit, or discontinued earlier.

For all analyses, all data available at the time of the analysis will be included. If any of the above-mentioned analyses coincide, the analyses will be combined. Additional interim analyses may be performed for safety and/or immunogenicity to facilitate decision making with regards to the planning of future studies. Unblinded data at the group level will be available for a limited number of sponsor personnel involved in the interim and primary analyses. An unblinded statistician, not otherwise involved in the study will prepare data presentations when unblinding at the participant level is required. Participants, clinical staff, and study-site personnel will remain blinded to the study vaccine allocation until the end of study. In addition, an unblinded statistician, not otherwise involved in the study, will monitor the number and severity of molecularly confirmed COVID-19 cases in the Ad26COVS1 and placebo groups to identify an imbalance between groups if it occurs (see Statistical Analysis Plan).

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

[a] May be performed based on operational availability of data.

Figure 5: Interim and Primary Analyses



*May be performed based on operational availability of data.
**Analysis of VNA/ELISA may be performed before availability of Th1/Th2 data, which may not be available at the time of this analysis. Vaccination of participants in Cohorts 2 or 3 will not be initiated without confirmation of a Th1-type response.
ADCP = antibody-dependent cellular phagocytosis; ELISA = enzyme-linked immunosorbent assay; Th = T-helper; VNA = virus neutralization assay

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	Adenovirus serotype 26
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AdVac®	adenoviral vaccine
AE	adverse event
BIDMC	Beth Israel Deaconess Medical Center
BMI	Body mass index
COA	clinical outcome assessment (paper or electronic as appropriate for this study)
COVID-19	coronavirus disease-2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CT	computed tomographic
d	day(s)
DBL	database lock
DNA	deoxyribonucleic acid
DRC	Data Review Committee
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ERD	enhanced respiratory disease
FAS	full analysis set
FDA	Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GLP	good laboratory practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular staining
IEC	Independent Ethics Committee
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
SIPPM	site investigational product and procedures manual
IM	intramuscular(ly)
IMP	Investigational Medicinal Product
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mo	month
MRU	medical resource utilization
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPI	per protocol immunogenicity
PQC	Product Quality Complaint
Pre-F	pre-fusion conformation-stabilized F protein
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
RNA	ribonucleic acid

RSV	respiratory syncytial virus
RT-PCR	reverse-transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SoA	Schedule of Activities
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
Th	T-helper
TNFα	tumor necrosis factor alpha
USP	United States Pharmacopeia
vac	vaccination
VNA	virus neutralization assay
WHO	World Health Organization

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

GCP 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 PI
- 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 PI, 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, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

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

10.2.2. 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.

10.2.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. 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 date and sign the ICF after the oral consent of the participant is obtained.

10.2.4. 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 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.

10.2.5. 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 Ad26COVS1, to understand SARS-CoV-2 infection, to understand differential vaccine responders, and to develop tests/assays related to Ad26COVS1 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, Withdrawal From the Use of Research Samples).

10.2.6. Committees Structure

Data Review Committee

An internal DRC, consisting of members that are not directly involved in the study conduct, data management, or statistical analysis, will be established and will monitor data to ensure the continuing safety of the participants enrolled in this study. The DRC will review data as indicated in Section 4.1, Overall Design. When appropriate, the conclusions of the DRC will be communicated to the investigators, the IRB/IEC, and the national regulatory authorities.

The DRC will specifically review safety data (solicited and unsolicited AEs and SAEs) 7-day post-first and post-second dose Cohorts 1a and 3 (in each of Cohort 1a and 3: a total of 15 participants including the 5 sentinels).

In addition, ad hoc review may be performed further to the occurrence of any AE/SAE leading to a study pausing situation as outlined in Section 6.9, Study Vaccination Pausing Rules, or at request of the sponsor's medical monitor or designee. The PI(s) and SRP/S will inform the DRC of any AE of concern.

The DRC will review blinded data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

It will also be possible for the DRC to review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions. If this is the case, a biomarker representative (not involved in the conduct of the study) will be part of the DRC.

This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DRC responsibilities, authorities, and procedures will be documented in its charter.

10.2.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding Ad26COVS1 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, including exploratory research 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 Ad26COVS1, 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 exploratory 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.

10.2.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report.

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 eCRF for accuracy and completeness during on-site 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.

10.2.9. 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 must be recorded in eCRF. 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 electronic CRF, 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.

All participative measurements (eg, questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF 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.

10.2.10. 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 medication; vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Participant- and investigator-completed scales and assessments designated by the sponsor ie, diary to record solicited AEs, daily signs and symptoms surveillance question, CSSI and global impression questions) will be recorded and will be considered source data. The participant's 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 eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.2.11. 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. 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 CRF 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 CRF 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.

10.2.12. 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 source documents, 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.

10.2.13. 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.

10.2.14. 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

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 International Conference on Harmonisation [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.

Any respiratory tract infection that is not due to SARS-CoV-2 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 any 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, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

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 judgment 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 one 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 serious and unexpected suspected adverse reaction 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 period if molecular testing indicates it is not a SARS-CoV-2 infection. If the molecular test is positive for SARS-CoV-2, the event should not be reported as an SAE. If molecular test results are not available within 24 hours of knowledge of the event, the event will be reported as an SAE, but will be subsequently downgraded from SAE status if it later turns out to be positive for SARS-CoV-2 by molecular testing.

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 Ad26COVS1, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.3.2. 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.

10.3.3. 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,[39] included in Appendix Toxicity Grading Scale.

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

The severity of solicited signs and symptoms will be graded in the diary by the participant based on the severity assessment provided in the diary and then verified 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]).

10.3.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- 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 intervention from breast-feeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

10.3.5. 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 adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

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 an SAE.

10.3.6. Product Quality Complaint Handling

Definition

A product quality complaint (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.

10.3.7. 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.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 one 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.

10.5. Appendix 5: 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).

A: Tables for Clinical Abnormalities

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 judgment 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	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

B: Tables for Laboratory Abnormalities

Laboratory tests may be performed during routine medical care and assessment of AEs or other medical events based on the investigator's judgment.

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** ULN is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

10.6. Appendix 6: Protocol Amendment History

This is an original protocol.

11. REFERENCES

1. Adenoviral Vaccine Safety Database V5.0. Janssen Vaccines & Prevention B.V. 10 April 2019.
2. Agrawal AS, Tao X, Algaissi A, et al. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. Hum Vaccin Immunother. 2016;12(9):2351-2356.
3. Anywaine Z, Whitworth H, Kaleebu P, et al. Safety and Immunogenicity of a 2-Dose Heterologous Vaccination Regimen With Ad26.ZEBOV and MVA-BN-Filo Ebola Vaccines: 12-Month Data From a Phase 1 Randomized Clinical Trial in Uganda and Tanzania. J Infect Dis. 2019;220(1):46-56.
4. Barouch DH, Liu J, Peter L, et al. Characterization of humoral and cellular immune responses elicited by a recombinant adenovirus serotype 26 HIV-1 Env vaccine in healthy adults (IPCAVD 001). J Infect Dis. 2013:207(2);248-256.
5. Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). Lancet. 2018;392(10143):232-243.
6. Belgian Red Cross. https://www.rodekruis.be/. Accessed 12 April 2020.
7. Bolles M, Deming D, Long K, et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85(23):12201-12215
8. Center for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) Symptoms and Complications. https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html. Accessed 15 February 2020.
9. Center for Disease Control and Prevention. Transcript - CDC Media Telebriefing: Update on COVID-19. https://www.cdc.gov/media/releases/2020/t0309-covid-19-update.html. Accessed 16 March 2020.
10. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin. Microbiol. Rev. 2015; 28(2):465–522.
11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
12. Chen Z, Zhang L, Qin C, et al. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J Virol. 2005;79(5):2678-2688.
13. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660-694.
14. Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol. 1969;89(4);449-463.
15. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Mar 2. doi: 10.1038/s41564-020-0695-z. [Epub ahead of print]
16. Deming D, Sheahan T, Heise M, et al. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. PLoS Med. 2006;3(12):e525.
17. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020 Mar 16. pii: e20200702. [Epub ahead of print]
18. European Centre for Disease Prevention and Control. Factsheet for health professionals on coronaviruses. https://www.ecdc.europa.eu/en/factsheet-health-professionals-coronaviruses. Accessed 15 February 2020.
19. Faber M, Lamirande EW, Roberts A, et al. A single immunization with a rhabdovirus-based vector expressing severe acute respiratory syndrome coronavirus (SARS-CoV) S protein results in the production of high levels of SARS-CoV-neutralizing antibodies. J Gen Virol. 2005;86(Pt 5):1435-1440.

20. Fulginiti VA, Eller JJ, Sieber OF, Joyner JW, Minamitani M, Meiklejohn G. Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. Am J Epidemiol. 1969:89(4);435-448.

21. Gidudu JK, Walco GA, Taddio A, et al./The Brighton Immunization Site Pain Working Group. Immunization site pain: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012:30(30);4558-4577.

22. Honda-okubo Y, Barnard D, Ong CH, Peng BH, Tseng CT, Petrovsky N. Severe acute respiratory syndrome-associated coronavirus vaccines formulated with delta inulin adjuvants provide enhanced protection while ameliorating lung eosinophilic immunopathology. J Virol. 2015;89(6):2995-3007.

23. Houser KV, Broadbent AJ, Gretebeck L, et al. Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody. PLoS Pathog. 2017;13(8):e1006565.

24. Investigator's Brochure: Ad26COVS1 (VAC31518), Edition 1.0. Janssen Vaccines & Prevention B.V.

25. Janssen Vaccines & Prevention B.V. Data on file.

26. Johns Hopkins CSSE. Coronavirus COVID-19 Global Cases. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed 8 March 2020.

27. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol. 1969:89;405-421.

28. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969:89(4);422-434.

29. Kohl KS, Walop W, Gidudu J, et al./The Brighton Collaboration Local Reaction Working Group for Swelling at or near Injection Site. Swelling at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine 2007:31;5858-5874.

30. Kohl KS, Walop W, Gidudu J, et al./The Brighton Collaboration Local Reaction Working Group for Induration at or near Injection Site. Induration at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine 2007:31;5839-5857.

31. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5:562–569.

32. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020 Jan 29. doi: 10.1056/NEJMoa2001316. [Epub ahead of print].

33. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Jan 30. pii: S0140-6736(20)30251-8.

34. Marcy SM, Kohl KS, Dagan R, et al./The Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004:22(5-6);551-556.

35. Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia ankara-vectored ebola vaccines: a randomized clinical trial. JAMA. 2016:315;1610-1623.

36. Modjarrad K, Roberts CC, Mills KT, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. Lancet Infect Dis. 2019;19(9):1013-1022.

37. Moghaddam A, Olszewska W, Wang B, et al. A potential molecular mechanism for hypersensitivity caused by formalin-inactivated vaccines. Nat Med. 2006:12(8);905-907.

38. Smatti MK, Al Thani AA, Yassine HM. Viral-Induced Enhanced Disease Illness. Front Microbiol. 2018;9:2991.

39. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. September 2007. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf. Accessed 19 February 2020.

40. US Department of Health and Human Services. Office for Human Research Protections - OHRP Expedited Review Categories. 1998. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categoriesof-research-expedited-review-procedure-1998/index.html. Accessed 24 February 2020.

41. US Food and Drug Administration. Conditions for IRB Use of Expedited Review. Federal Register: November 9, 1998 (Volume 63, Number 216). https://www.fda.gov/science-research/guidance-documentsincluding-information-sheets-and-notices/conditions-irb-use-expedited-review. Accessed 24 February 2020.

42. Wang D, Hu B, Hu C. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1585. [Epub ahead of print].

43. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). Accessed 15 February 2020.

44. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 12 March 2020.

45. World Health Organization. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations, October 2004. https://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1/en/. Accessed 15 February 2020.

46. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269.

47. Zhao J, Alshukairi AN, Baharoon SA, et al. Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. Sci Immunol. 2017;2(14). pii: eaan5393.

48. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.

49. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-347.

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 vaccine, 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

Signature: [electronic signature appended at the end of the protocol] 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.

Signature

User	Date	Reason

Janssen Vaccines & Prevention B.V.*

Clinical Protocol

Protocol Title

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26COVS1 in Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older

---

Protocol VAC31518COV1001; Phase 1/2a

Amendment 6

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(s):

IND: 22657
EudraCT NUMBER: 2020-001483-28

Status: Approved
Date: 19 September 2020
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-ERI-207834851, 7.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	19 September 2020
Amendment 5	13 August 2020
Amendment 4	6 August 2020
Amendment 3	8 July 2020
Amendment 2	5 June 2020
Amendment 1	20 May 2020
Original Protocol	4 May 2020

Amendment 6 (19 September 2020)

Overall Rationale for the Amendment: The Ad26.COV2.S dose level for Cohort 2a has been changed from 1×10^{11} virus particles (vp) to 5×10^{10} vp based on emerging data from Cohorts 1a, 1b and 3. In addition, **c**larifications on several issues have been made to align the study design with that of the proposed Phase 3 study VAC31518COV3001 and address health authority requests.

Section Number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 2.2 Background 3 Objectives and Endpoints 4.1 Overall Design 4.3 Justification for Dose	For Cohort 2a, the Ad26.COV2.S dose level has been changed from 1×10^{11} vp to 5×10^{10} vp.	The Ad26.COV2.S dose level for Cohort 2a has been adjusted to mimic the dosing regimen to be evaluated in study VAC31518COV3001.
1.3.3.1 Cohort 2a: Primary Regimen 1.3.4.1 Cohort 2b: Primary Regimen	A footnote that randomization and vaccination may occur on the same day has been added for Cohorts 2a and 2b.	Clarification on performing randomization and vaccination has been made.
1.1 Synopsis 1.3.6 Procedures for Participants with COVID-19-like Signs and Symptoms: footnote b 4.1 Overall Design 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms	It has been clarified in the protocol that the nasal swab sample should be taken by a health care professional, not only for study sites in Belgium as requested by the Ethics Committee (EC), but also for study sites in the US.	Based on regulatory agency feedback to align with the Belgian EC recommendation.
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.
5.1 Inclusion Criteria 5.2 Exclusion Criteria	Text was updated to clarify that participants enrolled in Cohort 3 may have mild hypertension, but not other comorbidities associated with an increased risk of severe COVID-19. Additionally, an inconsistency in footnote for Inclusion Criterion 5 has been corrected.	Based on regulatory agency feedback.

Section Number and Name	Description of Change	Brief Rationale
1.3.1 Cohort 1a: footnote g 1.3.2 Cohort 1b: footnote f 1.3.3.1 Cohort 2a: Primary Regimen: footnote f 1.3.3.2 Cohort 2a: Booster Vaccination: footnote d 1.3.4.1 Cohort 2b: Primary Regimen: footnote f 1.3.4.2 Cohort 2b: Booster Vaccination: footnote d 1.3.5 Cohort 3: footnote g 1.3.6 Procedures for Participants with COVID-19-like Signs and Symptoms: footnote d 8.2.2 Vital Signs	Text revised to align with wording in Section 8, Study Assessments and Procedures.	Alignment.
9.4.2 Primary Endpoints 10.4.1 Adverse Event Definitions and Classifications	It has been clarified that respiratory tract infections will be excluded from the (S)AE analyses if the molecular test is subsequently found to be positive for SARS-CoV-2.	Clarification on criteria and analysis of (S)AEs have been made.
9.5 Planned Analysis	Text was revised to clarify that data will be made publicly available.	The Sponsor plans to publish selected available group unblinded immunogenicity and blinded safety data for Cohorts 1a, 1b, and 3 for reasons of transparency since a large Phase 3 study will start based on this data. The Sponsor does however wish to reduce the potential for unblinding until the review of safety data 7 days after Dose 2 in Cohorts 1a, 1b, and 3 is completed at which time selected available group unblinded immunogenicity and safety data will be published. All participants and investigators will remain blinded to their treatment regimen until the end of the study.
10.6 Appendix 6: Toxicity Grading Scale	A minor error was corrected in the footnote of the Laboratory Abnormalities table.	Correction of minor error.
10.8.1 Case Definition for Moderate to Severe COVID-19 10.8.2 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 to simplify the moderate case definition based on feedback from regulatory agencies and partners.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26COVS1 in Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older

Ad26.COV2.S (also 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) virus spike (S) protein, which will be assessed in this study. This will be the first-in-human (FIH) study for Ad26.COV2.S.

OBJECTIVES AND ENDPOINTS

A description of study cohorts is provided in the Overall Design section below.

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels, 5×10^{10} virus particles (vp) and 1×10^{11} vp, administered intramuscularly (IM) as a single-dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	All participants in Cohorts 1, 2, and 3: • Solicited local and systemic adverse events (AEs) for 7 days after each vaccination in the primary regimen • Unsolicited AEs for 28 days after each vaccination in the primary regimen • For the primary endpoint: Serious adverse events (SAEs) from the first vaccination until 1 year after the second vaccination for Cohorts 1 and 3, and until 6 months after the primary regimen for Cohort 2

Objectives	Endpoints
Secondary	
• To assess the humoral and cellular immune response to Ad26.COV2.S	Humoral Immune Response All participants in Cohorts 1, 2, and 3: • SARS-CoV-2 neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay (VNA [wild-type virus and/or pseudovirion expressing S protein]) • SARS-CoV-2-binding antibodies measured by enzyme-linked immunosorbent assay (ELISA): Analysis of antibodies binding to the SARS-CoV-2 S protein. Cellular Immune Response A subset of participants in Cohorts 1, 2, and 3: • T-helper (Th)1 and Th2 immune responses as assessed by flow cytometry after SARS-CoV-2 S protein peptide stimulation of peripheral blood mononuclear cells (PBMCs) and intracellular staining [ICS] including CD4+/CD8+, interferon gamma [IFNγ], interleukin [IL] 2, tumor necrosis factor alpha [TNFα], IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.
Exploratory	
• To further assess the safety and reactogenicity of Ad26.COV2.S at a dose level of 5×10^{10} vp administered IM as a single booster vaccination at 6 months, 12 months, or 24 months after the primary regimen in healthy adults aged ≥18 to ≤55 years	All participants in Cohort 2: • Solicited local and systemic AEs for 7 days after each booster vaccination time point • Unsolicited AEs for 28 days after each booster vaccination time point • SAEs from the first booster vaccination time point until the end of the study

Objectives	Endpoints
• To further assess the humoral and cellular immune response to Ad26.COV2.S in various regimens	Humoral Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1 and 3: • SARS-CoV-2 neutralization as assessed by alternative SARS-CoV-2 neutralization assays (different from the VNA used for the secondary endpoint). • Adenovirus neutralization. • Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping). • Epitope-specificity characterization for B- and T-cells. • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. Cellular Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1, 2, and 3: • Single IFNγ and IL-4 enzyme-linked immunospot (ELISpot) assay after stimulation of PBMCs with SARS-CoV-2 S protein peptides. • Analysis of gene expression in cells stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells (ex vivo). • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells (ex vivo). A subset of participants in Cohort 2 only: • Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube-isolated PBMCs).
• To perform a preliminary analysis of vaccine efficacy in the prevention of molecularly confirmed coronavirus disease-2019 (COVID-19)	• The number of molecularly confirmed COVID-19 cases in Ad26.COV2.S versus placebo recipients in the overall study

Objectives	Endpoints
• To perform preliminary analysis of vaccine efficacy in the prevention of asymptomatic SARS-CoV-2 infection	• The number of participants with positive non-S protein ELISA (eg, N ELISA), if such an assay can be developed, in the Ad26.COV2.S and placebo groups
• To evaluate the presence of SARS-CoV-2 infection and the presence and severity of COVID-19 signs and symptoms	• Presence and severity of COVID-19 signs and symptoms • Confirmation of SARS-CoV-2 infection by molecular testing
• To examine the immune response in vaccinated individuals after natural infection and to explore other potentially informative biomarkers (eg, those associated with more severe disease)	• Confirmation of SARS-CoV-2 infection by molecular testing • SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein) • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein • Functional and molecular antibody characterization • Analysis of gene expression by RNA transcript profiling

Hypothesis

No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, reactogenicity, and immunogenicity endpoints.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, FIH 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, administered IM as a single dose or 2 dose schedule, with a single booster vaccination administered in one cohort.

The safety, reactogenicity, and immunogenicity will be evaluated in a cohort of adults aged ≥18 to ≤55 years. Safety, reactogenicity, and immunogenicity will also be evaluated in an expanded cohort in this age group. In addition, safety, reactogenicity, and immunogenicity will be evaluated in a cohort of adults aged ≥65 years.

The study includes the following cohorts:

1) Cohort 1:

   a. Cohort 1a: approximately 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.

c. Cohort 2: approximately 270 participants aged ≥18 to ≤55 years will be randomized to receive Ad26.COV2.S (approximately 240 participants) or a placebo (approximately 30 participants) in the primary regimen. Cohort 2 will include an evaluation of a single booster vaccination (see below for further details).

2) Cohort 3: approximately 375 participants (approximately 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: Vaccination Schedules

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	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 include an evaluation of a single booster vaccination (see below for further details).

N = number of participants; vp = virus particles.

An internal Data Review Committee (DRC) will be commissioned for this study to evaluate safety data over the course of the study and to review any events that meet a specific study pausing rule or any other safety issue that may arise.

Cohort 1 (Adults Aged ≥18 to ≤55 Years)

The first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) in Cohort 1a, enrolled at the same study site, to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. In Cohort 1a, as for each cohort, participants will be closely observed for a minimum of 1-hour post-vaccination for the development of acute reactions. A telephone call will be made to each of these 5 sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data, which will include solicited and unsolicited AEs and SAEs. The collected data will be reviewed in a blinded manner by the principal investigator (PI) and the sponsor's study responsible physician (SRP). Randomization and vaccination of additional participants will be halted until the review is completed.

In the absence of clinically significant findings from the review of 24-hour safety data from the first 5 sentinel participants, all participants in Cohort 1a and Cohort 1b will be randomized and vaccinated. The next 10 participants in Cohort 1a will be enrolled at the same study site as the 5 sentinel participants, randomly assigned to 1 of the 5 vaccination groups to have an overall 1:1:1:1:1 randomization ratio (ie, a total of 15 participants including the 5 sentinels, with 3 participants in each vaccination group), and administered the first vaccination. The DRC will review the blinded 3-day safety data (ie, from Day 1 to Day 4) and 7-day safety data (ie, from Day 1 to Day 8) following administration of the first vaccination to these first 15 participants, including solicited and unsolicited AEs and SAEs. In the absence of safety concerns, enrollment and vaccination of participants in Cohort 3 will begin.

Cohort 2 (Adults Aged ≥18 to ≤55 Years)

Cohort 2 will be initiated after the interim or primary analyses of Cohort 1a. In Cohort 2a, approximately 120 participants will receive Ad26.COV2.S at a dose level of 5×10^{10} vp and approximately 15 participants will receive a placebo in a single-dose primary regimen. In Cohort 2b, approximately 120 participants will receive Ad26.COV2.S at a dose level of 5×10^{10} vp and approximately 15 participants will receive a placebo in a 2-dose primary regimen. No staggered enrollment will be performed for Cohort 2; however, the DRC will evaluate safety data from Cohort 2 over the course of the study. If required, Cohort 2 may contribute to the safety database prior to initiation of larger studies.

If the immunogenicity results obtained after the 1st vaccination in Cohort 1a are not adequately supporting initiation of Cohort 2, then results obtained after the 2nd vaccination in the 2-dose regimens in Cohort 1a will be used to select the vaccine regimens to be evaluated in Cohort 2 of this study. If the immunogenicity results obtained after the 2nd vaccination in the 2-dose regimens in Cohort 1a do not demonstrate an adequately increased immune response, the sponsor will not provide the 2nd vaccination at Day 57 in Cohort 2b of this study.

In addition, data obtained after a single booster vaccination will be used to evaluate the effect of a booster vaccination at different time points and the duration of immune response (see below for further details).

Cohort 3 (Adults Aged ≥65 Years)

The safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adults aged ≥65 years will be assessed in Cohort 3. Vaccination of participants in Cohort 3 will begin after the DRC review of 7-day safety data from the first 15 participants in Cohort 1a if no safety concerns are identified.

In Cohort 3, the first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. A telephone call will be made to each of these 5 sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data, which will be reviewed in a

blinded manner by the PI and the sponsor's SRP. Randomization and vaccination of additional participants will be halted until the review is completed. In the absence of clinically significant findings, an additional 10 participants will be enrolled at the same study site as the 5 sentinel participants, randomly assigned to 1 of the 5 vaccination groups to have an overall 1:1:1:1:1 randomization ratio, and administered the first vaccination. The DRC will review the blinded 3-day safety data (ie, from Day 1 to Day 4) and 7-day safety data (ie, from Day 1 to Day 8) following administration of the first vaccination to these first 15 participants. Safety data for review will include solicited and unsolicited AEs and SAEs. In the absence of safety concerns, enrollment and vaccination of the remaining participants in Cohort 3 will proceed.

Single Booster Vaccination in Cohort 2

To gain preliminary insight into the safety and immunogenicity of a single booster vaccination, designated participants in Cohort 2 who received Ad26.COV2.S for the single-dose (Cohort 2a) or 2-dose (Cohort 2b) primary regimen will receive a single booster vaccination of Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the primary regimen, and will receive placebo at other applicable time points. As a control, a subgroup of participants who received Ad26.COV2.S for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen. In addition, participants who received placebo for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen. See the below tables for further details. An Ad26.COV2.S dose level of 5×10^{10} vp will be used for the booster vaccination in Cohorts 2a and 2b.

Table: Cohort 2a Vaccination Schedule – Primary Regimen and Single Booster Vaccination

		Primary Regimen	Booster Vaccination		
Group	N	Day 1 [a] (Vac 1)	6 months [b]	12 months [b]	24 months [b]
1	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Placebo
2	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo
3	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Ad26.COV2.S 5×10^{10} vp	Placebo
4	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Ad26.COV2.S 5×10^{10} vp
5	15	Placebo	Placebo	Placebo	Placebo
Total	**135**				

a. Study vaccine will be administered as a single-dose primary regimen.

b. Study vaccine (Ad26.COV2.S or a placebo) will be administered at 6 months, 12 months, and 24 months after completion of the single-dose primary regimen.

N = number of participants; vac = vaccination; vp = virus particles.

Table: Cohort 2b Vaccination Schedule – Primary Regimen and Single Booster Vaccination

		Primary Regimen		Booster Vaccination		
Group	N	Day 1 [a] (Vac 1)	Day 57 [a] (Vac 2)	8 months [b]	14 months [b]	26 months [b]
1	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Placebo
2	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo
3	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Ad26.COV2.S 5×10^{10} vp	Placebo
4	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Ad26.COV2.S 5×10^{10} vp
5	15	Placebo	Placebo	Placebo	Placebo	Placebo
Total	**135**					

a. Study vaccine will be administered as a 2-dose (Day 1 and Day 57) primary regimen.

b. Study vaccine (Ad26.COV2.S or a placebo) will be administered at 6 months, 12 months, and 24 months after completion of the 2-dose primary regimen. If the 2nd vaccination at Day 57 is not provided, then participants will follow the same SoA as Cohort 2a (ie, booster vaccination at 6, 12, and 24 months after completion of the single-dose primary regimen).

N = number of participants; vac = vaccination; vp = virus particles.

Procedures in Case of COVID-19-like Signs and Symptoms

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. If a participant experiences COVID-19-like symptoms, the following should take place:

- Participants should contact the study site at the time of symptom onset.
- A nasal swab should be collected by a health care professional from the participant at home (using available material for home swabs) or at the study site as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms and stored appropriately. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by molecular testing using the nasal swab sample.
- Participants should complete the Symptoms of Infection with Coronavirus-19 (SIC) and record their highest body temperature daily starting on the first day they experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.
- For participants with a positive test result for SARS-CoV-2 infection, a study visit will be conducted 28 days after symptom onset to assess the clinical course of the infection, record concomitant medications since symptom onset, and obtain a blood sample for evaluation of the immune response and other biomarkers.

NUMBER OF PARTICIPANTS

Overall, a target of approximately 1,045 adult male and female participants aged ≥18 to ≤55 years or ≥65 years will be randomly assigned in this study.

DOSAGE AND ADMINISTRATION

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 as a suspension in single-use vials, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp and 1×10^{11} vp
- Placebo: 0.9% NaCl solution

For blinding purposes, the same volume will be administered to all participants in a cohort.

IMMUNOGENICITY EVALUATIONS

Blood for evaluation of humoral and cellular immune responses will be drawn from participants at the time points specified in the Schedule of Activities. Immunogenicity assessments may include, but are not limited to, the humoral and cellular immunogenicity assays (as available and feasible) summarized in the below table.

Table : Summary of Immunogenicity Assays

Assay	Purpose
Humoral Immunogenicity	
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 (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S protein and, if such an assay can be developed, SARS-CoV-2 N protein
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other strain), as measured by an alternative neutralization assay (different from the VNA used for the secondary endpoint)
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Cellular Immunogenicity	
Flow cytometry (ICS)	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by ICS including $CD4^+/CD8^+$, IFNγ, IL-2,TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers
ELISpot	IFNγ and IL-4 responses to SARS-CoV-2 S protein peptides by PBMCs, based on single ELISpot
Gene expression analysis	Analysis of gene expression by RNA transcript profiling and/or analysis of protein translates, in cells or whole blood stimulated with SARS-CoV-2 S protein peptides or in unstimulated cells or whole blood (ex vivo)
Cytokine profiling (ELISA or multiplexed arrays)	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells or whole blood stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells or whole blood, by ELISA or multiplexed arrays and confirmation by functional in vitro assays

Assay	Purpose
T and B cell phenotyping	Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube isolated PBMCs)

ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot (assay); ICS = intracellular cytokine staining; IFNγ = interferon gamma; Ig = immunoglobulin; IL = interleukin; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha; VNA = virus neutralization assay.

SAFETY EVALUATIONS

After each vaccination, participants will remain under observation at the study site for at least 1 hour for the presence of any acute reactions and solicited events. Participants will be asked to note in the 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).

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. Participants will also be instructed on how to note signs and symptoms in the 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, and myalgia.

AEs and special reporting situations, whether serious or non-serious, 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. All other unsolicited AEs will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. All other SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) will be reported from the moment of first vaccination until completion of the participant's last study-related procedure.

STATISTICAL METHODS

Sample Size Calculation

The number of participants chosen for this study will provide a preliminary safety and immunogenicity assessment. While mild-to-moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. When 75 and 120 participants are vaccinated, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 3.9% and <2.5% respectively.

Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

FAS: The full analysis set will include all participants with at least one vaccine administration documented.

PPI: The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural infection occurring after screening (if applicable) will be excluded from the analysis set.

PPE: The per protocol efficacy population will include all randomized participants having received at least 1 vaccination for whom efficacy data concerning endpoint measures are available. All efficacy analyses will be done according to the as treated principle (ie, actually received vaccinations).

Primary Endpoint

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group. In addition, for selected tables, tabulations pooled by vaccine dose will also be provided. All safety analyses will be made on the FAS.

Secondary Endpoints

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval, or median and interquartile range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters at all available time points. Graphical representations of immunologic parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

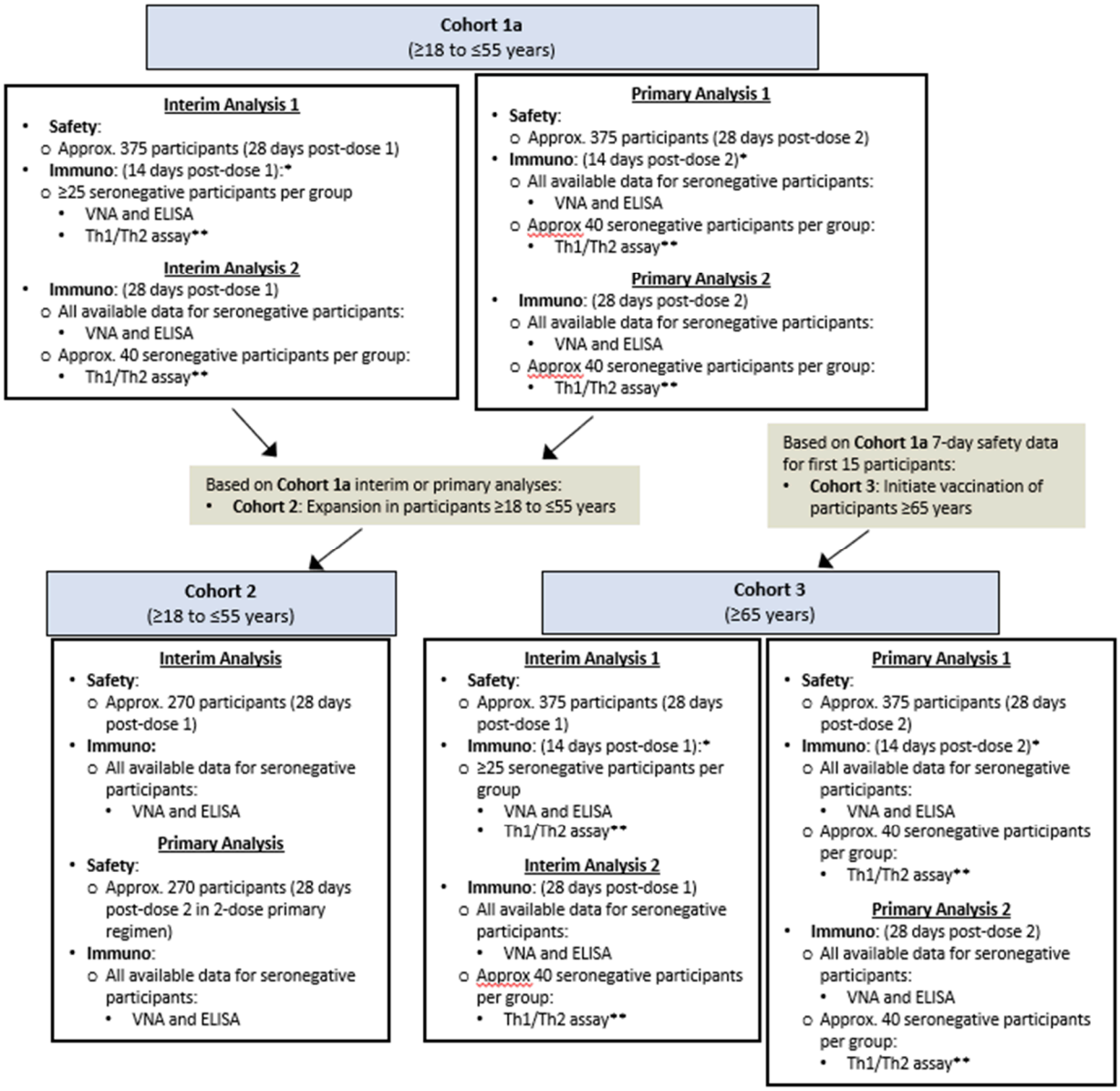
In addition, the ratio between neutralizing and binding antibodies as determined by VNA and S protein ELISA, respectively, will be calculated.

The immunogenicity analyses will be performed on the PPI population. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols).

Planned Analyses

Interim and primary analyses for each cohort are presented in the figure below.

Figure: Interim and Primary Analyses



*May be performed based on operational availability of data.
**Analysis of VNA/ELISA may be performed before availability of Th1/Th2 data, which may not be available at the time of this analysis.
ELISA = enzyme-linked immunosorbent assay; Th = T-helper; VNA = virus neutralization assay

The final analysis will be performed when the last participant from Cohorts 1a and 3 completes the final visit (12 months after second study vaccination) or discontinues earlier. It will include any data for Cohorts 1a and 3 that were not available for the interim and primary analyses and all data that are available for Cohorts 1b and 2 (including any data after booster vaccination). It will also include data from participants in each cohort who were seropositive for SARS-CoV-2-specific antibodies at screening.

The end-of-study analysis will be performed when all included participants have completed the last visit or last booster vaccination follow-up visit or discontinued earlier.

1.2. Schema

Figure 1: Schematic Overview of Cohort 1a

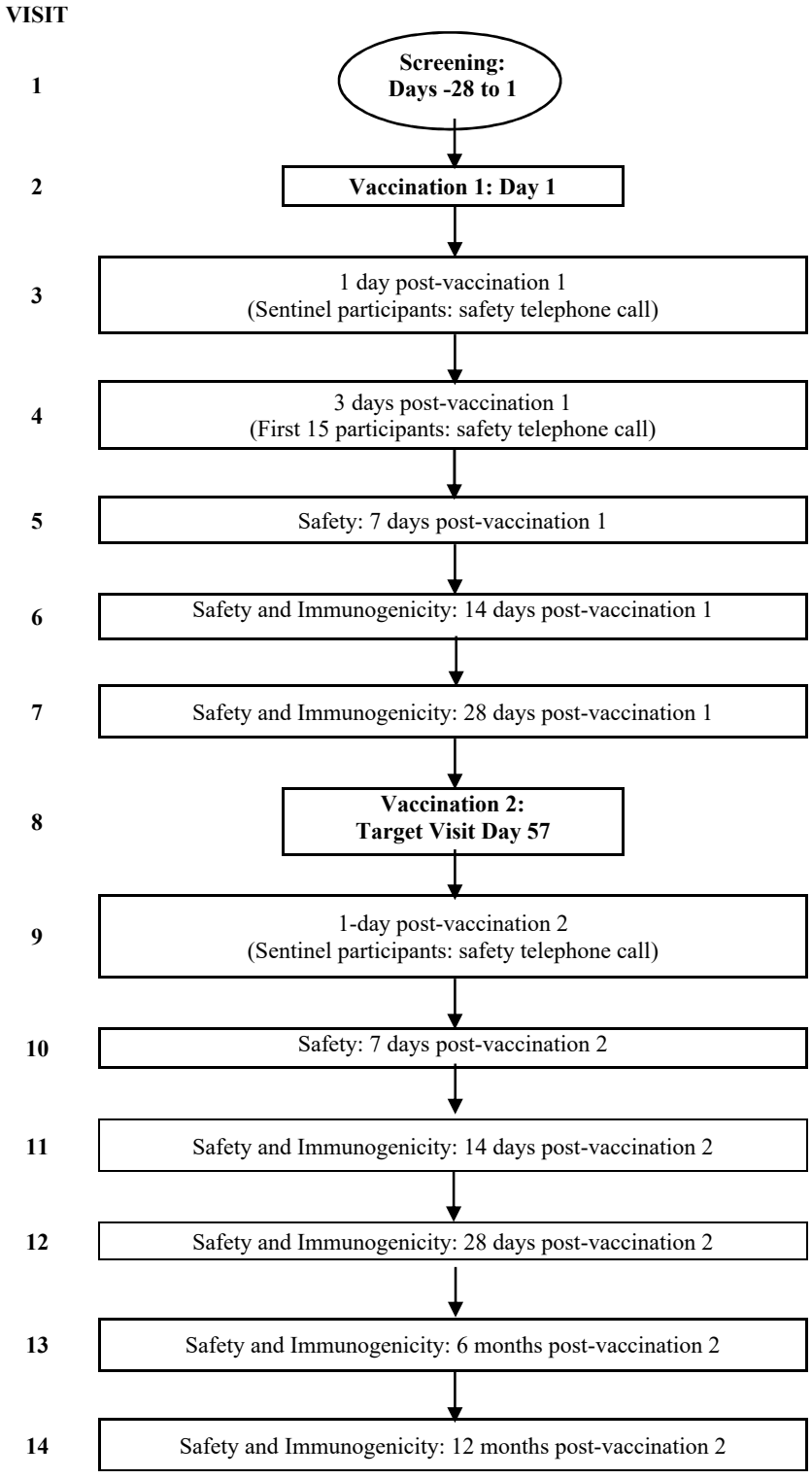


Figure 2: Schematic Overview of Cohort 1b

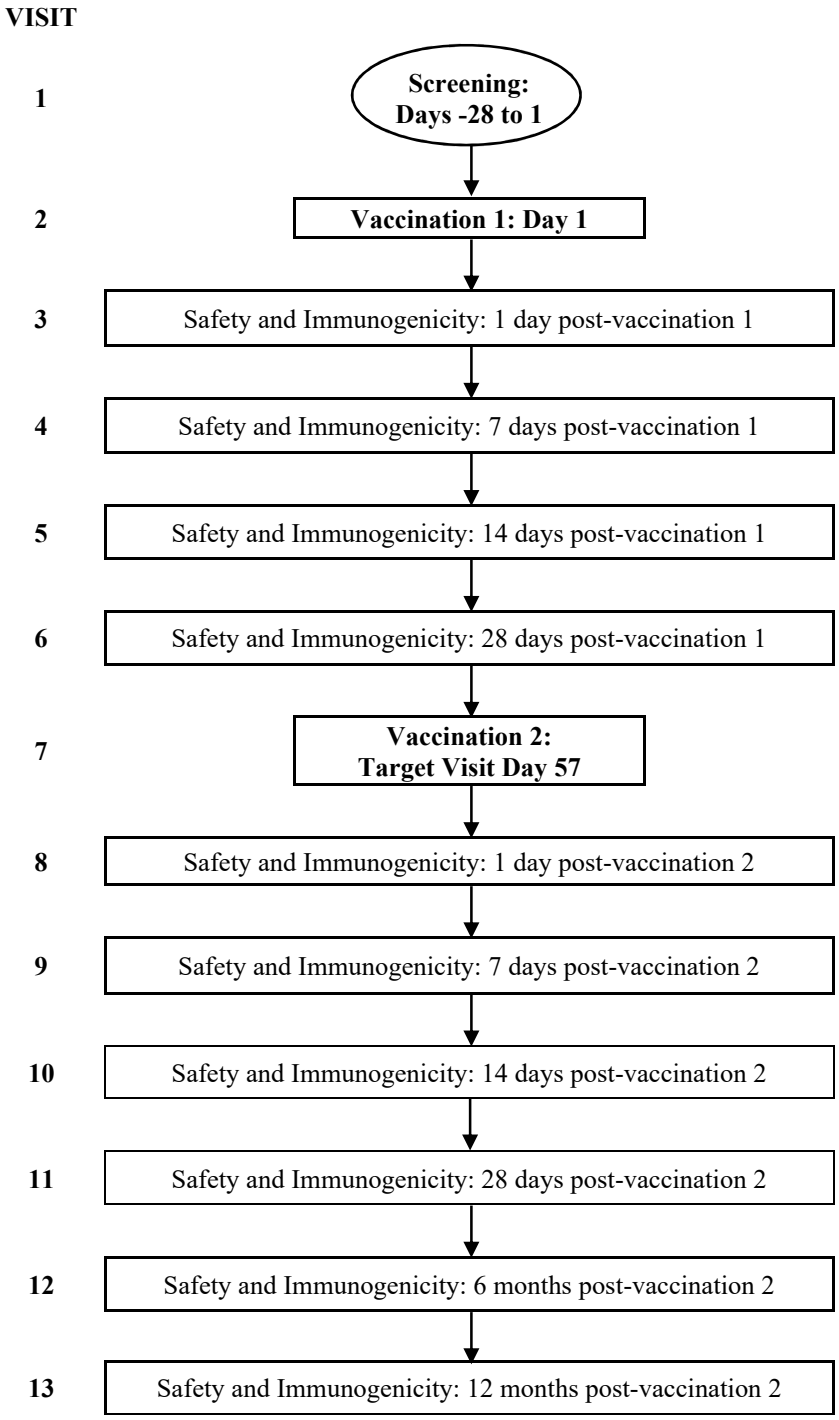
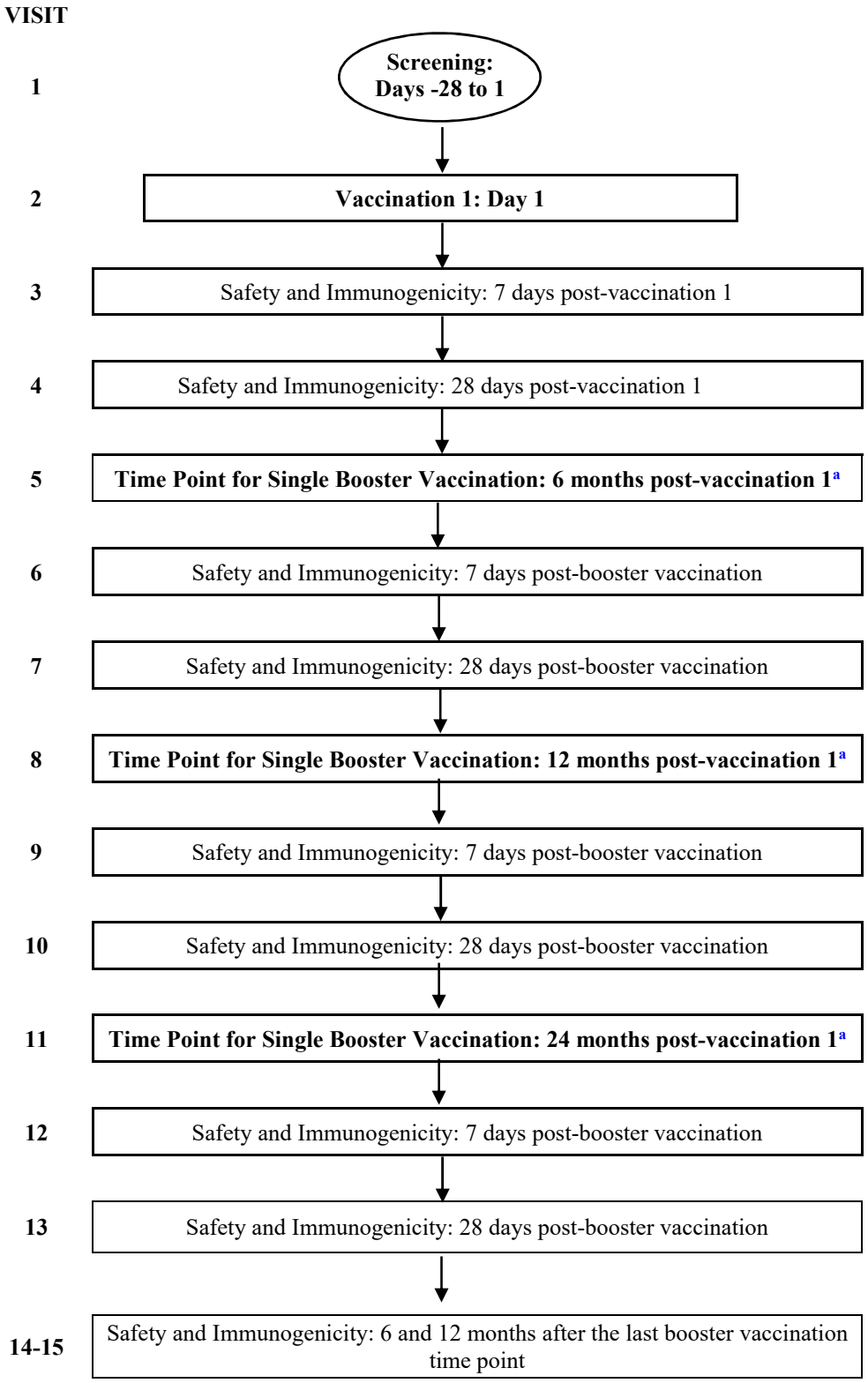
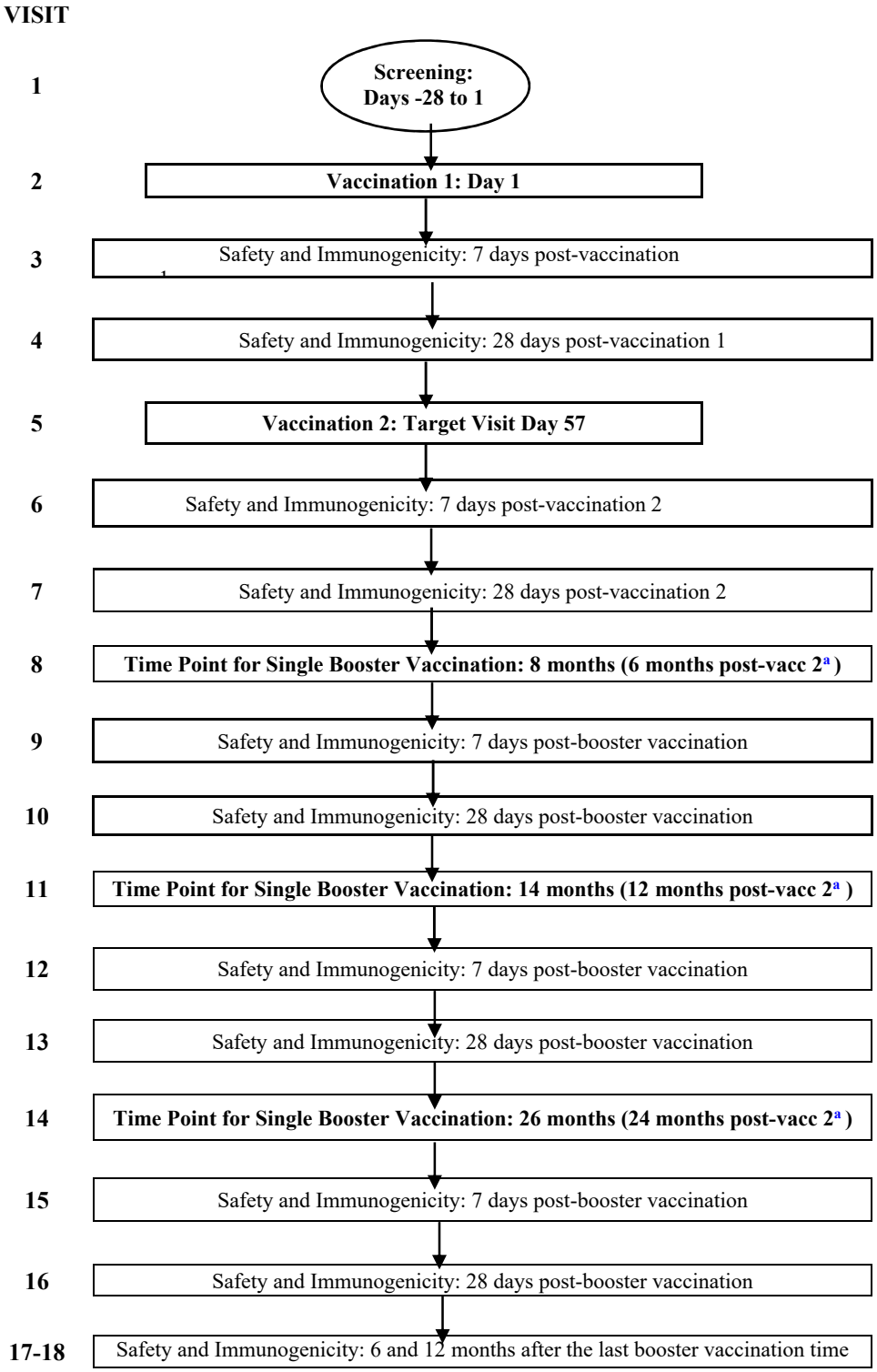


Figure 3: Schematic Overview of Cohort 2a



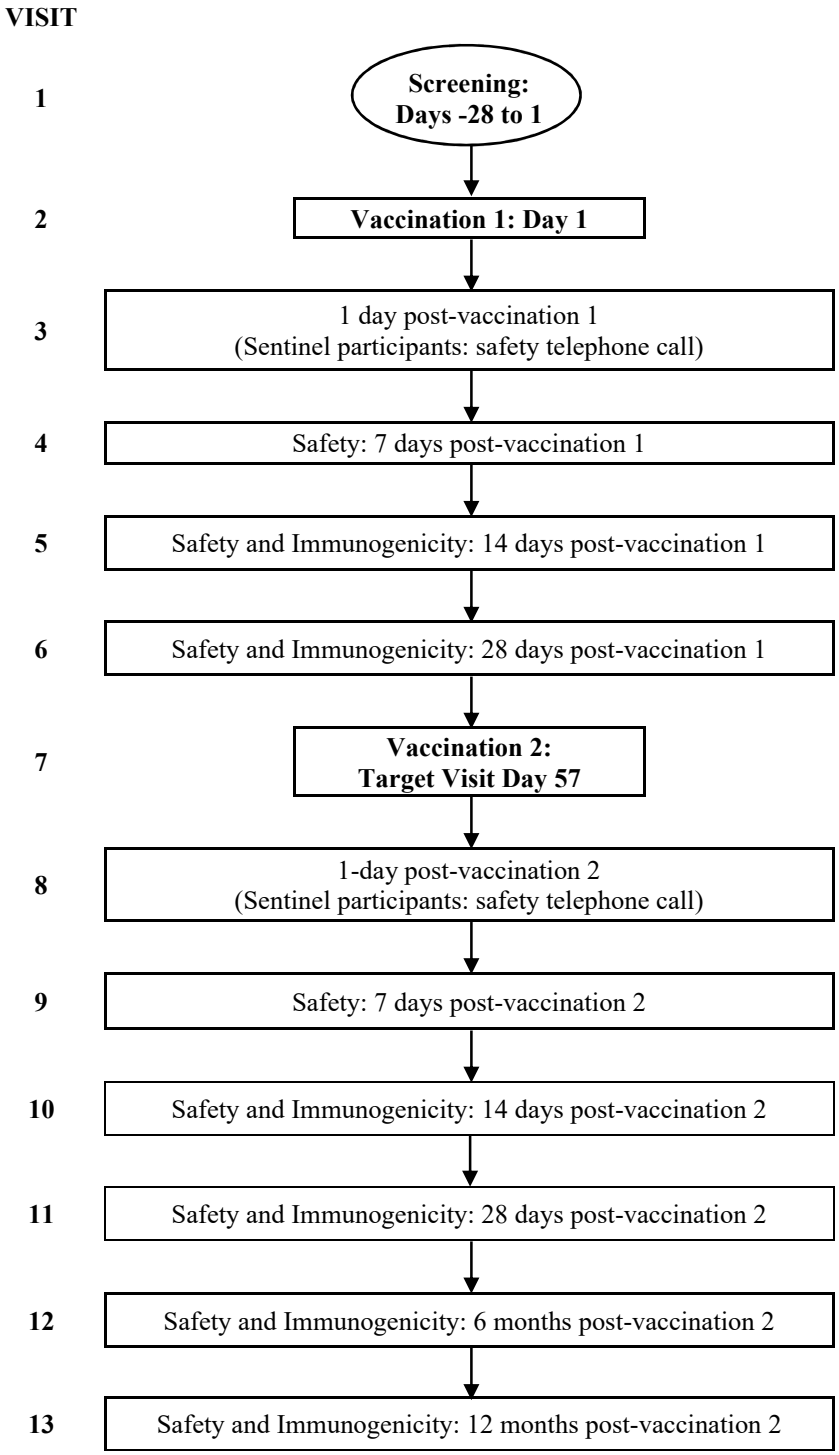
a. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the single-dose primary regimen and will receive placebo at the other indicated time points. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

Figure 4: Schematic Overview of Cohort 2b



a. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 8 months, 14 months, and 26 months (ie, 6 months, 12 months, or 24 months after completion of the 2-dose primary regimen) and will receive placebo at the other indicated time points. If the 2nd vaccination at Day 57 is not provided, then participants will follow the same SoA as Cohort 2a (ie, booster vaccination at 6, 12, and 24 months after completion of the single-dose primary regimen). Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 3 for further details.

Figure 5: Schematic Overview of Cohort 3



1.3. Schedule of Activities (SoA)

1.3.1. Cohort 1a

Phase	Screening [a]	Study Period													
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 3 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 2 +12 mo	
Target Visit Day ±Window	-28 to 1	1	2	4	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239* ±21	422* ±21	
Visit Type	Screening	Vaccine 1	(Safety tel.) [d]	(Safety tel.) [d]	Safety	Safety and Immuno		Vaccine 2	(Safety tel.) [d]	Safety	Safety and Immuno				Early Exit
Written informed consent [e]	●														
Inclusion/exclusion criteria	●	❶													
Demographics	●														
Medical history/prestudy meds	●	●													
Physical examination [f]	●														
Vital signs [g] incl. body temperature	●	❷			●	●	●	❷		●	●	●			❹
Nasal swab sample	❼	❽													
Serological test for SARS-CoV-2-specific antibodies	●	❽													
Randomization		❶													
Prevaccination symptoms [h]		❶						❶							
Urine pregnancy test [i]	●	❶						❶							
Clinical lab blood sample, mL	● 10	❽ 10			● 10			❶ 10		● 10					
Urinalysis	●	❽			●			❶		●					
Humoral immunity (serum), mL		❶ 30				● 30	● 30	❶ 30			● 30	● 30	● 30	● 30	❸ 20
Cellular immunity (PBMC), mL [j]		❶ 60				● 60	● 60	❶ 60			● 60	● 60	● 60	● 60	❸ 60
Cellular immunity (whole blood, PAXgene® tubes),mL [k]		❶ 2.5				● 2.5	● 2.5	❶ 2.5			● 2.5	● 2.5			
Vaccination		●						●							
1-hour post-vaccination observation [l]		●						●							
Solicited AE recording		*- - - - - Continuous- - - - -*						*- - - - - Continuous- - - - -*							❹
Unsolicited AE recording [m]		*- - - - - Continuous through +28 d- - - - -*						*- - - - - Continuous through +28 d- - - - -*							❺
SAE recording [n]		*- - - - - Continuous- - - - -*													●

Phase	Screening [a]	Study Period													
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Exit [b]**
Visit Timing		**Vac 1**	**Vac 1 + 1 d**	**Vac 1 + 3 d**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 1 d**	**Vac 2 + 7 d**	**Vac 2 + 14 d**	**Vac 2 + 28 d**	**Vac 2 + 6 mo**	**Vac 2 +12 mo**	
Target Visit Day ±Window	**-28 to 1**	**1**	**2**	**4**	**8±2 [c]**	**15±3**	**29±3**	**57-3/+7**	**58***	**64*±2 [c]**	**71*±3**	**85*±3**	**239* ±21**	**422* ±21**	
Visit Type	**Screening**	**Vaccine 1**	**(Safety tel.) [d]**	**(Safety tel.) [d]**	**Safety**	**Safety and Immuno**		**Vaccine 2**	**(Safety tel.) [d]**	**Safety**	**Safety and Immuno**				**Early Exit**
Concomitant meds [o]		*Continuous*													●
Participant diary distribution [p]		●						●							
Participant diary review [q]			❻	❻	●				❻	●					
Training and distribution: nasal swab kit and symptom surveillance booklet		●													
Signs and symptoms surveillance [r]		*Continuous*													
Approx. daily blood draw, mL: Participants at selected sites [j] [Participants not at selected sites]	10 [10]	102.5 [42.5]	- [-]	- [-]	10 [10]	92.5 [30]	92.5 [30]	102.5 [40]	- [-]	10 [10]	92.5 [30]	92.5 [30]	90 [30]	90 [30]	80 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [j] [Participants not at selected sites]	10 [10]	112.5 [52.5]	112.5 [52.5]	112.5 [52.5]	122.5 [62.5]	215 [92.5]	307.5 [122.5]	410 [162.5]	410 [162.5]	420 [172.5]	512.5 [202.5]	605 [232.5]	695 [262.5]	**785 [292.5]**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ check of diary during the telephone call; ❼ screening diagnostic test for SARS-CoV-2 infection will be performed locally; ❽ to be repeated pre-vaccination if the screening test was done more than 4 days before Day 1.

* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 14, 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).

c. If a participant comes in early for Visit 5 or 10, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Telephone contact on Day 2 and Day 58 for the 5 sentinel participants. Telephone contact on Day 4 for the first 15 participants including the 5 sentinel participants.

e. Signing of the ICF should be done before any study-related activity.

f. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
g. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
h. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 4). 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. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.
i. For women of childbearing potential only.
j. Samples to be taken from approximately 200 seronegative participants at selected sites.
k. Sample to be taken from all participants pre-vaccination on Day 1. At subsequent time points, samples to be taken only from approximately 200 seronegative participants at selected sites.
l. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
m. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
n. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
o. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
p. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
q. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
r. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; tel = telephone contact; vac = vaccination.

1.3.2. Cohort 1b

Phase	Screening [a]	Study Period												
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 2 + 12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	422*±21	
Visit Type	Screening	Vaccine 1	Safety and Immuno				Vaccine 2	Safety and Immuno						Early Exit
Written informed consent [d]	●													
Inclusion/exclusion criteria	●	❶												
Demographics	●													
Medical history/prestudy meds	●	●												
Physical examination [e]	●													
Vital signs [f] incl. body temperature	●	❷	●	●	●	●	❷	●	●	●	●			❹
Nasal swab sample	❻	❼												
Serological test for SARS-CoV-2-specific antibodies	●	❼												
Randomization		❶												
Prevaccination symptoms [g]		❶					❶							
Urine pregnancy test [h]	●	❶					❶							
Clinical lab blood sample, mL	● 10	❼ 10		● 10			❶ 10		● 10					
Urinalysis	●	❼		●			❶		●					
Humoral immunity (serum), mL		❶ 40	● 20	● 40	● 40	● 40	❶ 20	● 20	● 40	● 40	● 40	● 20	● 20	❸ 20
Cellular immunity (PBMC), mL		❶ 60		● 60	● 60	● 60	❶ 60		● 60	● 60	● 60	● 60	● 60	❸ 60
Cellular immunity (whole blood, PAXgene® tubes), mL		❶ 2.5	● 2.5	● 2.5			❶ 2.5	● 2.5	● 2.5					
Vaccination		●					●							
1 hour post-vaccination observation [i]		●					●							
Solicited AE recording		----- *Continuous*-----			❹		----- *Continuous*-----							❹
Unsolicited AE recording [j]		----- *Continuous through +28 d*-----					❺							❺
SAE recording [k]		----- *Continuous*-----												●
Concomitant meds [l]		----- *Continuous*-----												●
Participant diary distribution [m]		●					●							
Participant diary review [n]			●	●				●	●					

Phase	Screening [a]	Study Period												
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 2 + 12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	422*±21	
Visit Type	Screening	Vaccine 1	Safety and Immuno				Vaccine 2	Safety and Immuno						Early Exit
Training and distribution: nasal swab kit and symptom surveillance booklet		●												
Signs and symptoms surveillance [o]		*Continuous*												
Approx. daily blood draw, mL:	10	112.5	22.5	112.5	100	100	92.5	22.5	112.5	100	100	80	80	80
Approx. cumulative blood draw, mL:	10	122.5	145	257.5	357.5	457.5	550	572.5	685	785	885	965	**1,045**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ Screening diagnostic test for SARS-CoV-2 infection will be performed locally; ❼ to be repeated pre-vaccination if the screening test was done more than 4 days before Day 1.

* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 13, 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).

c. If a participant comes in early for Visit 4 or 9, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Signing of the ICF should be done before any study-related activity.

e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

f. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.

g. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 5). 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. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.

h. For women of childbearing potential only.

i. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
j. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
k. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
l. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
m. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
n. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
o. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-Cov-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination.

1.3.3. Cohort 2a

1.3.3.1. Primary Regimen

Phase	Screening [a]	Study Period			
Visit #	1	2	3	4	Exit [b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	
Target Visit Day ±Window	-28 to 1	1	8±2 [c]	29±3	
Visit Type	**Screening**	**Vaccine 1**	**Safety and Immuno**		**Early Exit**
Written informed consent [d]	●				
Inclusion/exclusion criteria	●	❶			
Demographics	●				
Medical history/prestudy meds	●	●			
Physical examination [e]	●				
Vital signs [f] incl. body temperature	●	❷	●	●	❹
Nasal swab sample	❻	❼			
Serological test for SARS-CoV-2-specific antibodies	●	❼			
Randomization [s]		❶			
Prevaccination symptoms [g]		❶			
Urine pregnancy test [h]	●	❶			
Clinical lab blood sample, mL	● 10	❼ 10	● 10		
Urinalysis	●	❼	●		
Humoral immunity (serum), mL		❶ 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [i]		❶ 60		● 60	❸ 60
Cellular immunity (whole blood, PAXgene tubes), mL [j]		❶ 2.5	● 2.5	● 2.5	❸ 2.5
Smart Tube sample (whole blood), mL [i]		❶ 4		● 4	❽ 4
Vaccination [s]		●			
1 hour post-vaccination observation [k]		●			
Solicited AE recording [l]		*Cont +7d*			❹
Unsolicited AE recording [m]		*- - - - Continuous through +28 d- - -*			❺
SAE recording [n]		*- - - -- - - - -- - - - -- - - - - Continuous- - - - -- - - - -- - - - -- - - - -*			●
Concomitant meds [o]		*- - - -- - - - -- - - - -- - - - - Continuous- - - - -- - - - -- - - - -- - - - -*			●
Participant diary distribution [p]		●			
Participant diary review [q]			●		

Phase	Screening [a]	Study Period			
Visit #	1	2	3	4	Exit [b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	
Target Visit Day ±Window	-28 to 1	1	8±2 [c]	29±3	
Visit Type	Screening	Vaccine 1	Safety and Immuno		Early Exit
Training and distribution: nasal swab kit and symptom surveillance booklet		●			
Signs and symptoms surveillance [r]		- - - - *Continuous* - - - -			
Approx. daily blood draw, mL: Participants at selected sites [i] [Other participants]	10 [10]	106.5 [42.5]	42.5 [40]	96.5 [30]	86.5 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [i] [Other participants]	10 [10]	116.5 [52.5]	159 [92.5]	255.5 [122.5]	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ Screening diagnostic test for SARS-CoV-2 infection will be performed locally; ❼ to be repeated pre-vaccination if the screening test was done more than 4 days before Day 1; ❽ Smart Tube sample will only be taken if the early exit is at least 10 days after the previous Smart Tube sample.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.
b. For those participants who are unable to continue participation in the study up to Visit 4, 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).
c. If a participant comes in early for Visit 3, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.
d. Signing of the ICF should be done before any study-related activity.
e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
f. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
g. 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 at the scheduled time for vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.
h. For women of childbearing potential only.
i. Samples will be collected from 27 seronegative participants at selected sites.

j. Sample to be taken from all participants pre-vaccination on Day 1. At subsequent time points, samples to be taken only from 27 seronegative participants at selected sites.
k. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
l. Participants will record solicited symptoms in a diary for 7 days post-vaccination.
m. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
n. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
o. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
p. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
q. If an event is still ongoing on Day 8, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
r. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms.
s. Vaccination and randomization may be done on the same day.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination.

1.3.3.2. Booster Vaccination

Phase	Study Period											
Visit #	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Exit** [a]
Visit Timing	**Vac 1 + 6 mo**	**Booster +7 d**	**Booster +28 d**	**Vac 1 + 12 mo**	**Booster +7 d**	**Booster + 28 d**	**Vac 1 + 24 mo**	**Booster +7 d**	**Booster + 28 d**	**Booster + 6 mo**	**Booster + 12 mo**	
Target Visit Day ±Window	**183±21**	**190*±2** [b]	**211*±3**	**366±21**	**373*±2** [b]	**394*±3**	**731±21**	**738*±2** [b]	**759*±3**	**913*±21**	**1,096*±21**	
Visit Type	**Booster** [c]	**Safety and Immuno**		**Booster** [c]	**Safety and Immuno**		**Booster** [c]	**Safety and Immuno**				**Early Exit**
Vital signs [d] incl. body temperature	❷	●	●	❷	●	●	❷	●	●			❺
Prevaccination symptoms [e]	❶			❶			❶					
Urine pregnancy test [f]	❶			❶			❶					
Humoral immunity (serum), mL	❶ 30	● 30	● 30	❶ 30	● 30	● 30	❶ 30	● 30	● 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [g]				❶ 60								❹ 60
Cellular immunity (whole blood, PAXgene tubes), mL [g]		● 2.5			● 2.5			● 2.5				❼ 2.5
Vaccination	●			●			●					
1-hour post-vaccination observation [h]	●			●			●					
Solicited AE recording [i]	*Cont +7d*			*Cont +7d*			*Cont +7d*					❺
Unsolicited AE recording [j]	*- - - - Continuous through +28 d- - - -*			*- - - - Continuous through +28 d- - -*			*- - - - - Continuous through +28 d- - - -*					❻
SAE recording [k]	*- Continuous- -*											●
Concomitant meds [l]	*- Continuous- -*											●
Participant diary distribution	●			●			●					
Participant diary review [m]		●			●			●				
Signs and symptoms surveillance [n]	*- - - - - - - - - - - - - - Continuous- - - - - - - - - -*											
Approx. daily blood draw, mL: Participants at selected sites [g] [Other participants]	30 [30]	32.5 [30]	30 [30]	90 [30]	32.5 [30]	30 [30]	30 [30]	32.5 [30]	30 [30]	30 [30]	30 [30]	82.5 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [g] [Other participants]	285.5 [152.5]	318 [182.5]	348 [212.5]	438 [242.5]	470.5 [272.5]	500.5 [302.5]	530.5 [332.5]	563 [362.5]	593 [392.5]	**623 [422.5]**	**653 [452.5]**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood sample for humoral immunogenicity will only be taken if the early exit visit is at least 10 days after the previous humoral immunogenicity blood draw; ❹ blood sample for cellular immunogenicity (PBMC) will only be taken if the early exit visit coincides with or is before Visit 8 and is at least 10 days after the previous cellular immunogenicity (PBMC) blood draw; ❺ if within 7 days of the previous vaccination; ❻ if within 28 days of the previous vaccination; ❼ whole blood sample (PAXgene tube) will only be taken if the early exit visit coincides with or is before Visit 12 and is at least 10 days after the previous whole blood sample (PAXgene tube).

*The timings of visits after a booster vaccination will be determined relative to the actual day of that vaccination.

a. For those participants who are unable to continue participation in the study up to Visit 14, 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).
b. If a participant comes in early for Visit 6, 9, or 12, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.
c. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the primary regimen and will receive placebo at the other applicable time points. Participants not designated to receive a single booster vaccination will receive placebo at each applicable time regimen. See Table 2 for further details.
d. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
e. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 6). 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. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.
f. For women of childbearing potential only.
g. Samples will be collected from 27 seronegative participants at selected sites.
h. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
i. Participants will record solicited symptoms in a diary for 7 days post-vaccination.
j. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
k. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
l. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
m. If an event is still ongoing on Day 190, Day 373, or Day 738, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

n. Through 1 year after completion of the primary regimen, if a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms. At 1 year after completion of the primary regimen, the need for, and level of, surveillance and follow-up for signs and symptoms will be re-evaluated based on the status of the COVID-19 pandemic. Continued recording of signs and symptoms of COVID-19 until study end may be required.

AE = adverse event; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination

1.3.4. Cohort 2b

1.3.4.1. Primary Regimen

Phase	Screening [a]			Study Period				
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Exit [b]**
Visit Timing		**Vac 1**	**Vac 1 + 7 d**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 7 d**	**Vac 2 + 28 d**	
Target Visit Day ±Window	**-28 to 1**	**1**	**8±2 [c]**	**29±3**	**57-3/+7**	**64*±2 [c]**	**85*±3**	
Visit Type	**Screening**	**Vaccine 1**	**Safety and Immuno**		**Vaccine 2**	**Safety and Immuno**		**Early Exit**
Written informed consent [d]	●							
Inclusion/exclusion criteria	●	❶						
Demographics	●							
Medical history/prestudy meds	●	●						
Physical examination [e]	●							
Vital signs [f] incl. body temperature	●	❷	●	●	❷	●	●	❹
Nasal swab sample	❻	❼						
Serological test for SARS-CoV-2-specific antibodies	●	❼						
Randomization [s]		❶						
Prevaccination symptoms [g]		❶			❶			
Urine pregnancy test [h]	●	❶			❶			
Clinical lab blood sample, mL	● 10	❼ 10	● 10		❶ 10	● 10		
Urinalysis	●	❼	●		❶	●		
Humoral immunity (serum), mL		❶ 30	● 30	● 30	❶ 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [i]		❶ 60		● 60	❶ 60		● 60	❸ 60
Cellular immunity (whole blood, PAXgene tubes), mL [j]		❶ 2.5	● 2.5	● 2.5	❶ 2.5	● 2.5	● 2.5	❸ 2.5
Smart Tube sample (whole blood), mL [i]		❶ 4		● 4				❽ 4
Vaccination [s]		●			●			
1-hour post-vaccination observation [k]		●			●			
Solicited AE recording [l]		*Cont +7d*			*Cont +7d*			❹
Unsolicited AE recording [m]		*- - - - Continuous through +28 d- - -*			*-- - - Continuous through +28 d- - -*			❺
SAE recording [n]		*- - - - - - - - - - - - - Continuous- - - - - - - - - - - - - -*						●
Concomitant meds [o]		*- - - - - - - - - - - - - Continuous- - - - - - - - - - - - - -*						●
Participant diary distribution [p]		●			●			
Participant diary review [q]			●			●		

Phase	Screening [a]			Study Period				
Visit #	1	2	3	4	5	6	7	Exit [b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 2	Vac 2 + 7 d	Vac 2 + 28 d	
Target Visit Day ±Window	-28 to 1	1	8±2 [c]	29±3	57-3/+7	64*±2 [c]	85*±3	
Visit Type	Screening	Vaccine 1	Safety and Immuno		Vaccine 2	Safety and Immuno		Early Exit
Training and distribution: nasal swab kit and symptom surveillance booklet		●						
Signs and symptoms surveillance [r]		- *Continuous* -						
Approx. daily blood draw, mL: Participants at selected sites [i] [Other participants]	10 [10]	106.5 [42.5]	42.5 [40]	96.5 [30]	102.5 [40]	42.5 [40]	92.5 [30]	86.5 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [i] [Other participants]	10 [10]	116.5 [52.5]	159 [92.5]	255.5 [122.5]	358 [162.5]	400.5 [202.5]	493 [232.5]	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ Screening diagnostic test for SARS-CoV-2 infection will be performed locally; ❼ to be repeated pre-vaccination if the screening test was done more than 4 days before Day 1; ❽ Smart Tube sample will only be taken if the early exit visit is at least 10 days after the previous Smart Tube sample.

* The timings of the visit after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 7, 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).

c. If a participant comes in early for Visit 3 or 6, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Signing of the ICF should be done before any study-related activity.

e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

f. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.

g. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 7). 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. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.

h. For women of childbearing potential only.

i. Samples will be collected from 27 seronegative participants at selected sites.
j. Sample to be taken from all participants pre-vaccination on Day 1. At subsequent time points, samples to be taken only from 27 seronegative participants at selected sites.
k. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
l. Participants will record solicited symptoms in a diary for 7 days post-vaccination.
m. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
n. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
o. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
p. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
q. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
r. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms.
s. Vaccination and randomization may be done on the same day.

AE = adverse event; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination

1.3.4.2. Booster Vaccination

Phase	Study Period											
Visit #	8	9	10	11	12	13	14	15	16	17	18	Exit [a]
Visit Timing	Vac 2 + 6 mo	Booster +7 d	Booster +28 d	Vac 2 + 12 mo	Booster +7 d	Booster + 28 d	Vac 2 + 24 mo	Booster +7 d	Booster + 28 d	Booster + 6 mo	Booster + 12 mo	
Target Visit Day ±Window	239*±21	246*±2 [b]	267*±3	422*±21	429*±2 [b]	450*±3	787*±21	794*±2 [b]	815*±3	969*±21	1,152*±21	
Visit Type	Booster [c]	Safety and Immuno		Booster [c]	Safety and Immuno		Booster [c]	Safety and Immuno				Early Exit
Vital signs [d] incl. body temperature	❷	●	●	❷	●	●	❷	●	●			❺
Prevaccination symptoms[e]	❶			❶			❶					
Urine pregnancy test [f]	❶			❶			❶					
Humoral immunity (serum), mL	❶ 30	● 30	● 30	❶ 30	● 30	● 30	❶ 30	● 30	● 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [g]				❶ 60								❹ 60
Cellular immunity (whole blood, PAXgene tubes), mL [g]		● 2.5			● 2.5			● 2.5				❼ 2.5
Vaccination	●			●			●					
1-hour post-vaccination observation [h]	●			●			●					
Solicited AE recording [i]	*Cont +7d*			*Cont +7d*			*Cont +7d*					❺
Unsolicited AE recording [j]	*- - - - Continuous through +28 d- - - -*			*- - - - Continuous through +28 d- - - -*			*- - - - Continuous through +28 d- - - -*					❻
SAE recording [k]	*- Continuous- -*											●
Concomitant meds [l]	*- Continuous- -*											●
Participant diary distribution	●			●			●					
Participant diary review [m]		●			●			●				
Signs and symptoms surveillance [n]	*- - - - - - - - - - - - Continuous- - - - - - - - - -*											
Approx. daily blood draw, mL: Participants at selected sites [g] [Other participants]	30 [30]	32.5 [30]	30 [30]	90 [30]	32.5 [30]	30 [30]	30 [30]	32.5 [30]	30 [30]	30 [30]	30 [30]	82.5 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [g] [Other participants]	523 [262.5]	555.5 [292.5]	585.5 [322.5]	675.5 [352.5]	708 [382.5]	738 [412.5]	768 [442.5]	800.5 [472.5]	830.5 [502.5]	**860.5 [532.5]**	**890.5 [562.5]**	

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood sample for humoral immunogenicity will only be taken if the early exit visit is at least 10 days after the previous humoral immunogenicity blood draw; ❹ blood sample for cellular immunogenicity (PBMC) will only be taken if the early exit visit coincides with or is before Visit 11 and at least 10 days after the

previous cellular immunogenicity (PBMC) blood draw; ❺ if within 7 days of the previous vaccination; ❻ if within 28 days of the previous vaccination; ❼ whole blood sample (PAXgene tube) will only be taken if the early exit visit coincides with or is before Visit 15 and is at least 10 days after the previous whole blood sample (PAXgene tube).

*The timings of visits after the second vaccination or a booster vaccination will be determined relative to the actual day of that vaccination.

a. For those participants who are unable to continue participation in the study up to Visit 17, 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).
b. If a participant comes in early for Visit 9, 12, or 15, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.
c. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the 2-dose primary regimen and will receive placebo at the other applicable time points. If the 2nd vaccination at Day 57 is not provided, then participants will follow the same SoA as Cohort 2a (ie, booster vaccination at 6, 12, and 24 months after completion of the single-dose primary regimen). Participants not designated to receive a single booster vaccination will receive placebo at each applicable time point. See Table 3 for further details.
d. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
e. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 7). 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. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.
f. For women of childbearing potential only.
g. Samples will be collected from 27 seronegative participants at selected sites.
h. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
i. Participants will record solicited symptoms in a diary for 7 days post-vaccination.
j. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
k. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
l. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
m. If an event is still ongoing on Day 246, Day 429, or Day 794, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
n. Through 1 year after completion of the primary regimen, if a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms. At 1 year after completion of the primary regimen, the need for, and level of, surveillance and follow-up

for signs and symptoms will be re-evaluated based on the status of the COVID-19 pandemic. Continued recording of signs and symptoms of COVID-19 until study end may be required.

AE = adverse event; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination

1.3.5. Cohort 3

Phase	Screening [a]	Study Period												
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 2 + 12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	422*±21	
Visit Type	Screening	Vaccine 1	(Safety tel.) [d]	Safety	Safety and Immuno		Vaccine 2	(Safety tel.) [d]	Safety	Safety and Immuno				Early Exit
Written informed consent [e]	●													
Inclusion/exclusion criteria	●	❶												
Demographics	●													
Medical history/prestudy meds	●	●												
Physical examination [f]	●													
Vital signs [g] incl. body temperature	●	❷		●	●	●	❷		●	●	●			❹
Nasal swab sample	❼	❽												
Serological test for SARS-CoV-2-specific antibodies	●	❽												
Randomization		❶												
Prevaccination symptoms [h]		❶					❶							
Clinical lab blood sample, mL	● 10	❽ 10		● 10			❶ 10		● 10					
Urinalysis	●	❽		●			❶		●					
Humoral immunity (serum), mL		❶ 30			● 30	● 30	❶ 30			● 30	● 30	● 30	● 30	❸ 20
Cellular immunity (PBMC), mL, [i]		❶ 60			● 60	● 60	❶ 60			● 60	● 60	● 60	● 60	❸ 60
Cellular immunity (whole blood, PAXgene® tubes), mL [j]		❶ 2.5			● 2.5	● 2.5	❶ 2.5			● 2.5	● 2.5			
Vaccination		●					●							
1-hour post-vaccination observation [k]		●					●							
Solicited AE recording		*----- Continuous-----*					*----- Continuous-----*							❹
Unsolicited AE recording [l]		*----- Continuous through +28 d-----*					*----- Continuous through +28 d-----*							❺
SAE recording [m]		*----- Continuous-----*												●
Concomitant meds [n]		*----- Continuous-----*												●
Participant diary distribution [o]		●					●							
Participant diary review [p]			❻	●				❻	●					

Phase	Screening [a]	Study Period												
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	Exit [b]
Visit Timing		Vac 1	Vac 1 + 1 d	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 1 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 2 + 12 mo	
Target Visit Day ±Window	-28 to 1	1	2	8±2 [c]	15±3	29±3	57-3/+7	58*	64*±2 [c]	71*±3	85*±3	239*±21	422*±21	
Visit Type	Screening	Vaccine 1	(Safety tel.) [d]	Safety	Safety and Immuno		Vaccine 2	(Safety tel.) [d]	Safety	Safety and Immuno				Early Exit
Training and distribution: nasal swab kit and symptom surveillance booklet		●												
Signs and symptoms surveillance [q]		- Continuous- -												
Approx. daily blood draw, mL Participants at selected sites [i] [Participants not at selected sites]	10 [10]	102.5 [42.5]	- [-]	10 [10]	92.5 [30]	92.5 [30]	102.5 [40]	- [-]	10 [10]	92.5 [30]	92.5 [30]	90 [30]	90 [30]	80 [20]
Approx. cumulative blood draw, mL Participants at selected sites [i] [Participants not at selected sites]	10 [10]	112.5 [52.5]	112.5 [52.5]	122.5 [62.5]	215 [92.5]	307.5 [122.5]	410 [162.5]	410 [162.5]	420 [172.5]	512.5 [202.5]	605 [232.5]	695 [262.5]	**785 [292.5]**	-

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ❹ if within 7 days of the previous vaccination; ❺ if within 28 days of the previous vaccination; ❻ check of diary during the telephone call; ❼ Screening diagnostic test for SARS-CoV-2 infection will be performed locally; ❽ to be repeated pre-vaccination if the screening test was done more than 4 days before Day 1.

* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

b. For those participants who are unable to continue participation in the study up to Visit 13, 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).

c. If a participant comes in early for Visit 4 or 9, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit.

d. Telephone contact on Day 2 and Day 58 for the 5 sentinel participants.

e. Signing of the ICF should be done before any study-related activity.

f. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

g. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.

h. 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 at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows (see Section 5.5 and Table 8). 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. In addition, the investigator must check the criteria for withdrawal of study vaccinations as noted in Section 7.1.
i. Samples to be taken from approximately 200 seronegative participants at selected sites.
j. Sample to be taken from all participants pre-vaccination on Day 1. At subsequent time points, samples to be taken only from approximately 200 seronegative participants at selected sites.
k. Participants will be closely observed for a minimum of 1-hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
l. AEs and special reporting situations 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. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post-vaccination.
m. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants 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 for all participants from the moment of first vaccination until completion of the participant's last study-related procedure.
n. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
o. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
p. If an event is still ongoing on Day 8 or Day 64, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
q. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; mo = months; SAE = serious adverse event; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; tel = telephone contact; vac = vaccination

1.3.6. Procedures for Participants with COVID-19-like Signs and Symptoms

Timing relative to onset of signs and symptoms	Day 1	Days 1-4	Days 3-8	Day 29 ± 7d [a]	Until resolution
Participant to contact study site as soon as any signs or symptoms of possible COVID-19 occur	●				
Nasal swab [b]		●	❶		
Physical examination [c]				●	
Vital signs [d] including body temperature				●	
Record concomitant medications since symptom onset				●	
Humoral immunity (serum), mL				● 15	
RNA-seq (whole blood, PAXgene tube)				● 2.5	
Body temperature [e]		❷			
Symptoms of Infection with Coronavirus-19 (SIC) [f]		❷			
Study-site personnel to contact participant [g]		*Weekly or more frequently*			

❶ A second nasal swab will be obtained 2 to 4 days after the first swab. ❷ If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.

a. A study visit will be conducted 28 days (±7 days) after the onset of symptoms for participants with a positive test result for SARS-CoV-2 infection.
b. A nasal swab should be collected by a health care professional from the participant at home (using available material for home swabs) or at the study site as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms (see Section 8.1.2.1, Prespecified Criteria for Suspected COVID-19). The sample should be transferred to the study site by an appropriate method as soon as possible after collection.
c. An abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
d. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperature will be measured preferably via the oral route.
e. Participant should measure body temperature daily and record the highest temperature each day.
f. Participants should complete the SIC starting on the first day they experience symptoms (See Section 10.7, Appendix 7, for an example of the SIC).
g. If a participant has a positive test result for SARS-CoV-2 infection, the participant may be requested to remain at home and not visit the study site. If necessary, study-site personnel will visit the participant at home. 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.

COVID-19 = coronavirus disease-2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

2. INTRODUCTION

Ad26.COV2.S (also 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) virus spike (S) protein, which will be assessed in this study. This will be the first-in-human (FIH) study for Ad26.COV2.S.

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.[27]

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

COVID-19 Vaccine and Considerations

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

Although the quantitative correlate of protection against SARS-CoV-2 infection has not yet been identified, neutralizing antibody responses against the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) S protein have been associated with protection against experimental SARS-CoV and MERS-CoV infection in nonclinical models.[14,50] 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.[34,36,51] 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, Risks Related to Study Participation).

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 one 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), Fc-mediated antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) (HIV, Malaria). Furthermore, these data support an immunogenicity profile with emphasis on T-helper (Th)1 responses and demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in $CD4^+$ and $CD8^+$ T cells.[4,28,38]

Ad26.COV2.S Candidate Vaccine

The aim of the COVID-19 vaccine clinical development program is to develop a safe and efficacious vaccine for the prevention of COVID-19. The initial effort will be to rapidly demonstrate safety and immunogenicity in adults aged ≤55 years, in order to initiate an efficacy trial 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 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.[14,21,39] The 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.[52]

2.1. Study Rationale

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[17,49] It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019.[35] Epidemiological investigations indicated 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.[35] 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.[36,49] 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.[36]

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 January 30, 2020, and declared the outbreak to be a pandemic on March 11, 2020.[46,47] As of April 29, 2020, approximately 3,170,000 cases of COVID-19 had been reported.[29]

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.[9] Severe clinical presentations have been reported in as many as 20–25% of laboratory-confirmed cases.[20] 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%).[13] 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%).[43] 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 because of complications, including acute respiratory distress syndrome, arrhythmia, and shock.

At present, it appears that individuals aged 65 years or older, especially those with comorbid diseases, are subject to the highest incidence of morbidity and mortality.[23] 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.[19] 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). Consistent with these findings was a study of 149,082 COVID-19 cases reported in the US.[11] Although persons aged <18 years account for 22% of the US population, only 1.7% of these cases occurred in this age group. 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.

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.[36] The first known cases of severe acute respiratory syndrome (SARS) occurred in Southern China in November 2002.[48] 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.[52] MERS-CoV is considered to be a zoonotic virus capable of non-sustained 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 Middle East respiratory syndrome (MERS) present with various clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory disease with extrapulmonary manifestations.[12,52] 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.[12,48] The case-fatality rate of MERS-CoV infections is estimated to be 35%.[12]

Therefore, while the understanding of the epidemiology and clinical spectrum of COVID-19 is still evolving during the ongoing pandemic, the current knowledge of the disease burden highlights the urgent medical need for a prophylactic vaccine.

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 Phase 1/2a clinical study. Details of the nonclinical immunogenicity of Ad26.COV2.S are provided in the IB.[27]

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 profile 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} virus particles (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).

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. At the time of protocol Amendment 6 writing, the 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 Cohort 2a of this Phase 1 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, and filovirus.

As of 27 March 2020, Ad26-based vaccines had been administered to approximately 67,000 participants in ongoing and completed studies, including more than 50,000 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, cutoff 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 27 March 2020, more than 62,000 participants were enrolled in ongoing studies. 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 cutoff 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, Risks Related to Study Participation 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 with 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 cutoff date of 27 October 2019, more than 3,600 participants aged ≥60 years received an Ad26.RSV.preF-based regimen in completed and ongoing studies. An acceptable safety and tolerability 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.

T-helper (Th)1/Th2 Profile of Ad26-based Vaccines in Clinical Studies

In the 1960s, a formalin-inactivated (FI) 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.[16,22,30,31] 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.[40] Vaccine-induced ERD has also been described for SARS-CoV and MERS-CoV in animal models.[41]

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 IFNγ and TNFα production in CD4+ and CD8+ T cells.[3,4,5] 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 primary analysis 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.[27]

2.3.1. Risks Related to Study Participation

This clinical study is a FIH study for Ad26.COV2.S. The following potential risks for Ad26.COV2.S will be monitored during the study and are specified in the protocol:

Risks Related to Ad26.COV2.S

At the time of protocol Amendment 6 writing, initial immunogenicity and safety data were available (Section 2.2). For the most comprehensive nonclinical information regarding Ad26.COV2.S, refer to the latest version of the IB and its addenda (if applicable).[27]

Sites should advice 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 emerging data from Cohorts 1a and 3 that became available at the time of writing of protocol Amendment 6.

Risks Related to Adenoviral-vectored Vaccines

The clinical AdVac® safety database (report version 5.0, dated 10 April 2020, cutoff 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, Background, 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 adverse events (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 4-11 years, and 24.8% of children aged 12-17 years after vaccination with an Ad26-based vaccine. For placebo, these percentages were 29.2% in children aged 4-11 years and 14.3% in children aged 12-17 years. No children aged 1-3 years have received placebo.

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

There was a trend towards 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 1-3 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 4-11 years (reported in ≥15% of Ad26 participants) were headache (23.6%; no data are available for the placebo arm 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 12-17 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 towards 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).

In children for Ad26, the most frequently reported unsolicited AE was malaria,[a] reported in 36.8% of children aged 1-3 years, in 19.0% of children aged 4-11 years, and in 10.6% of children aged 12-17 years. One child in the 12-17 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 4-11 years [vs. 4.2% with placebo] and 2.4% of children aged 12-17 years [vs. 4.8% with placebo]). No AEs in children aged 1-3 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 a 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 allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine), will be excluded from the study.

After each vaccination, participants will remain at the study site for at least 1 hour and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

Pregnancy and Birth Control

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

Women of childbearing potential will be required to agree to practicing a highly effective method of contraception and agree to remain on such a method of contraception from signing the informed consent form (ICF) until 3 months after the last dose of study vaccine (See Section 5.1, Inclusion

[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.

Criteria). Women who are pregnant or breast-feeding will be excluded from the study. Women who become pregnant while enrolled in the study will not receive further study vaccine but may continue other study procedures at the discretion of the investigator (see Section 7.1, Discontinuation of Study Vaccination).

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 Swabs

Collection of a nasal swab 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,[2,7,18,25,26] 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 ICF. The initial cohort in this study (Cohort 1a) will include healthy adults aged ≥18 to ≤55 years of age. 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, Section 8.1.2, and Section 10.8, Appendix 8, Case Definitions for COVID-19). 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, an unblinded statistician, not otherwise involved in the study, 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 unblinded statistician will inform the Data Review Committee (DRC) 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 DRC will be described in the Statistical Analysis Plan.

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, Study Population) 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 Schedule of Activities.
  - After each vaccination, participants will remain at the study site for at least 1 hour and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a diary to document solicited signs and symptoms. Details are provided in Section 8.2, Safety Assessments and Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting.
  - The investigator or the designee will document unsolicited AEs as indicated in Section 8.2, Safety Assessments; Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting; and Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.
  - 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.
- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - Eligibility will be reassessed pre-vaccination on Day 1.
  - Clinical laboratory assessment (blood and urine) will be performed at screening, pre-vaccination at each day of vaccination (pre-dose 1 and pre dose 2), and at the Day 7 post

vaccination visit for the primary regimens (Day 8 and Day 64). Details are provided in Section 10.2, Appendix 2, Clinical Laboratory Tests.

- In Cohorts 1a and 3, five sentinel participants will be evaluated for safety before extending enrollment in each cohort. The sentinel participants will be vaccinated at least 1 hour apart. A telephone call will be made to each of the sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data. The blinded 24-hour post-vaccination safety data in these sentinel participants will be reviewed by the principal investigator (PI) and sponsor's study responsible physician (SRP). Randomization and vaccination of additional participants will be halted until this 24-hour sentinel safety evaluation is completed. Refer to Section 4.1, Overall Design, for further details. For Cohorts 1a and 3, the second vaccination will be administered to the sentinel participants first. The PI and SRP will also review blinded safety data from the 5 sentinel participants following the second vaccination but randomization and vaccination of participants will not be halted during this review.
- For Cohorts 1a and 3, an internal DRC will review blinded[a] safety data following administration of the first vaccination to the first 15 participants. Refer to Section 4.1, Overall Design, for further details.
- There are prespecified rules for all participants, that if met would result in pausing of further vaccinations, preventing exposure of new participants to study vaccine until the DRC reviews all safety data (see Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations).
- Study vaccinations will be discontinued in participants for the reasons included in Section 7, Discontinuation of Study Vaccination and Participant Discontinuation/Withdrawal.
- Contraindications to vaccination are included in Section 5.5, Criteria for Temporarily Delaying Administration of Study Vaccination.

[a] The DRC will review blinded data first but may review unblinded data if deemed necessary.

3. OBJECTIVES AND ENDPOINTS

A description of study cohorts is provided in Section 4.1.

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM as a single-dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	All participants in Cohorts 1, 2, and 3: • Solicited local and systemic AEs for 7 days after each vaccination in the primary regimen • Unsolicited AEs for 28 days after each vaccination in the primary regimen • For the primary endpoint: Serious adverse events (SAEs) from the first vaccination until 1 year after the second vaccination for Cohorts 1 and 3, and until 6 months after the primary regimen for Cohort 2
Secondary	
• To assess the humoral and cellular immune response to Ad26.COV2.S	<u>Humoral Immune Response</u> All participants in Cohorts 1, 2, and 3: • SARS-CoV-2 neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay (VNA [wild-type virus and/or pseudovirion expressing S protein]) • SARS-CoV-2-binding antibodies measured by enzyme-linked immunosorbent assay (ELISA): Analysis of antibodies binding to the SARS-CoV-2 S protein. <u>Cellular Immune Response</u> A subset of participants in Cohorts 1, 2, and 3: • Th1 and Th2 immune responses as assessed by flow cytometry after SARS-CoV-2 S protein peptide stimulation of peripheral blood mononuclear cells (PBMCs) and intracellular staining [ICS] including CD4+/CD8+, IFNγ, interleukin [IL] 2, TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.
Exploratory	
• To further assess the safety and reactogenicity of Ad26.COV2.S at a dose level of 5×10^{10} vp administered IM as a single booster vaccination at 6 months, 12 months, or 24 months after the primary regimen in healthy adults aged ≥18 to ≤55 years	All participants in Cohort 2: • Solicited local and systemic AEs for 7 days after each booster vaccination time point • Unsolicited AEs for 28 days after each booster vaccination time point • SAEs from the first booster vaccination time point until the end of the study

Objectives	Endpoints
• To further assess the humoral and cellular immune response to Ad26.COV2.S in various regimens	Humoral Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1 and 3: • SARS-CoV-2 neutralization as assessed by alternative SARS-CoV-2 neutralization assays (different from the VNA used for the secondary endpoint). • Adenovirus neutralization. • Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping). • Epitope-specificity characterization for B- and T-cells. • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. Cellular Immune Response: Exploratory analyses may include the following assays for a subset of participants in Cohorts 1, 2, and 3: • Single IFNγ and IL-4 enzyme-linked immunospot (ELISpot) assay after stimulation of PBMCs with SARS-CoV-2 S protein peptides. • Analysis of gene expression in cells stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells (ex vivo). • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells (ex vivo). A subset of participants in Cohort 2 only: • Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube-isolated PBMCs).
• To perform a preliminary analysis of vaccine efficacy in the prevention of molecularly confirmed COVID-19	• The number of molecularly confirmed COVID-19 cases in Ad26.COV2.S versus placebo recipients in the overall study

Objectives	Endpoints
• To perform preliminary analysis of vaccine efficacy in the prevention of asymptomatic SARS-CoV-2 infection	• The number of participants with positive non-S protein ELISA (eg, N ELISA), if such an assay can be developed, in the Ad26.COV2.S and placebo groups
• To evaluate the presence of SARS-CoV-2 infection and the presence and severity of COVID-19 signs and symptoms	• Presence and severity of COVID-19 signs and symptoms • Confirmation of SARS-CoV-2 infection by molecular testing
• To examine the immune response in vaccinated individuals after natural infection and to explore other potentially informative biomarkers (eg, those associated with more severe disease)	• Confirmation of SARS-CoV-2 infection by molecular testing • SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein) • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein • Functional and molecular antibody characterization • Analysis of gene expression by RNA transcript profiling

HYPOTHESIS

No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, reactogenicity, and immunogenicity endpoints (see Section 9.4, Statistical Analyses).

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, FIH 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, administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in one cohort.

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

Participants will receive IM injections of Ad26.COV2.S or a placebo as shown in Table 1, Table 2, and Table 3. Two dose levels of Ad26.COV2.S will be administered: 5×10^{10} vp and 1×10^{11} vp.

The study includes the following cohorts:

1) Cohort 1:
    a. Cohort 1a: approximately 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: approximately 270 participants aged ≥18 to ≤55 years will be randomized to receive Ad26.COV2.S (approximately 240 participants) or a placebo (approximately 30 participants) in the primary regimen. Cohort 2 will include an evaluation of a single booster vaccination (see below for further details).
3) Cohort 3: approximately 375 participants (approximately 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

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	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 include an evaluation of a single booster vaccination (see Table 2 and Table 3 for further details).

N = number of participants; vp = virus particles.

An internal DRC will be commissioned for this study to evaluate safety data over the course of the study and to review any events that meet a specific study pausing rule or any other safety issue that may arise (see Section 6.9, Study Vaccination Pausing Rules). Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

In Cohorts 1a and 3, participants will be enrolled in a staggered approach with safety evaluations in place before extending enrollment within the cohort and progressing from one cohort to the next (Figure 6). A diagram of the study design is provided in Section 1.2, Schema.

Cohort 1 (Adults Aged ≥18 to ≤55 Years)

The first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) in Cohort 1a, enrolled at the same study site, to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour

apart. In Cohort 1a, as for each cohort, participants will be closely observed for a minimum of 1 hour post-vaccination for the development of acute reactions. A telephone call will be made to each of these 5 sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data, which will include solicited and unsolicited AEs and SAEs. The collected data will be reviewed in a blinded manner by the principal investigator (PI) and the sponsor's study responsible physician (SRP). Randomization and vaccination of additional participants will be halted until the review is completed.

In the absence of clinically significant findings from the review of 24-hour safety data from the first 5 sentinel participants, all participants in Cohort 1a and Cohort 1b will be randomized and vaccinated. The next 10 participants in Cohort 1a will be enrolled at the same study site as the 5 sentinel participants, randomly assigned to 1 of the 5 vaccination groups to have an overall 1:1:1:1:1 randomization ratio (ie, a total of 15 participants including the 5 sentinels, with 3 participants in each vaccination group), and administered the first vaccination. The DRC will review the blinded 3-day safety data (ie, from Day 1 to Day 4) and 7-day safety data (ie, from Day 1 to Day 8) following administration of the first vaccination to these first 15 participants, including solicited and unsolicited AEs and SAEs. In the absence of safety concerns, enrollment and vaccination of participants in Cohort 3 will begin.

Cohort 2 (Adults Aged ≥18 to ≤55 Years)

Cohort 2 will be initiated after interim or primary analyses of Cohort 1a. In Cohort 2a, approximately 120 participants will receive Ad26.COV2.S at a dose level of 5×10^{10} vp and approximately 15 participants will receive a placebo in a single-dose primary regimen. In Cohort 2b, approximately 120 participants will receive Ad26.COV2.S at a dose level of 5×10^{10} vp and approximately 15 participants will receive a placebo in a 2-dose primary regimen. No staggered enrollment will be performed for Cohort 2; however, the DRC will evaluate safety data from Cohort 2 over the course of the study. If required, Cohort 2 may contribute to the safety database prior to initiation of larger studies.

If the immunogenicity results obtained after the 1st vaccination in Cohort 1a are not adequately supporting initiation of Cohort 2, then results obtained after the 2nd vaccination in the 2-dose regimens in Cohort 1a will be used to select the vaccine regimens to be evaluated in Cohort 2 of this study. If the immunogenicity results obtained after the 2nd vaccination in the 2-dose regimens in Cohort 1a do not demonstrate an adequately increased immune response, the sponsor will not provide the 2nd vaccination at Day 57 in Cohort 2b of this study.

In addition, data obtained after a single booster vaccination will be used to evaluate the effect of a booster vaccination at different time points and the duration of immune response (see below for further details).

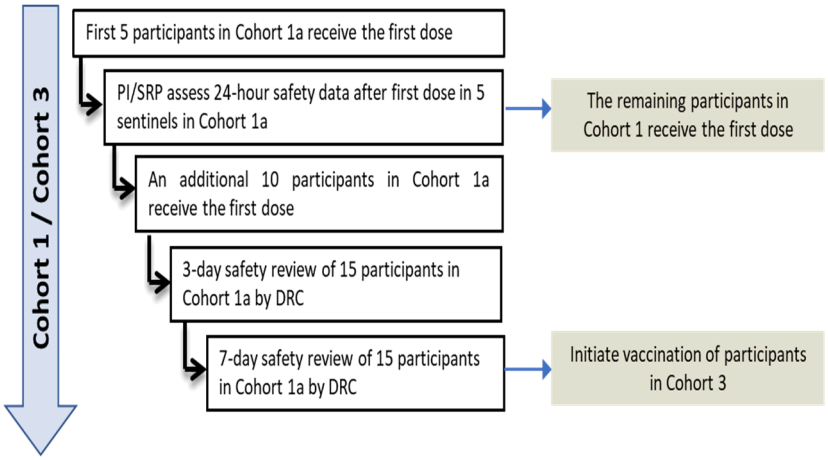
Cohort 3 (Adults Aged ≥65 Years)

The safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adults aged ≥65 years will be assessed in Cohort 3. Vaccination of participants in Cohort 3 will begin after the DRC review of 7-day safety data from the first 15 participants in Cohort 1a if no safety concerns are identified.

In Cohort 3, the first doses of study vaccine will be administered to a sentinel group of 5 participants (1 participant per group) to monitor for any unexpected severe adverse reactions. The sentinel participants will be vaccinated at least 1 hour apart. A telephone call will be made to each of these 5 sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data, which will be reviewed in a blinded manner by the PI and the sponsor's SRP. Randomization and vaccination of additional participants will be halted until the review is completed. In the absence of clinically significant findings, an additional 10 participants will be enrolled at the same study site as the 5 sentinel participants, randomly assigned to 1 of the 5 vaccination groups to have an overall 1:1:1:1:1 randomization ratio, and administered the first vaccination. The DRC will review the blinded 3-day safety data (ie, from Day 1 to Day 4) and 7 day safety data (ie, from Day 1 to Day 8) following administration of the first vaccination to these first 15 participants. Safety data for review will include solicited and unsolicited AEs and SAEs. In the absence of safety concerns, enrollment and vaccination of the remaining participants in Cohort 3 will proceed.

Although it is anticipated that an efficacy study will be initiated in adults aged ≥18 to ≤55 years, it is important to establish safety and a regimen capable of inducing appropriate immunity for this candidate vaccine in elderly adults aged ≥65 years, as this group displays the highest incidence of morbidity and mortality in the current pandemic caused by SARS-CoV-2.

Figure 6: Participant Enrollment and First Dose Safety Strategy in Cohorts 1 and 3



C = cohort; DRC = Data Review Committee; PI = principal investigator; SRP = study responsible physician

Single Booster Vaccination in Cohort 2

To gain preliminary insight into the safety and immunogenicity of a single booster vaccination, designated participants in Cohort 2 who received Ad26.COV2.S for the single-dose (Cohort 2a) or 2-dose (Cohort 2b) primary regimen will receive a single booster vaccination of Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the primary regimen, and will receive placebo at other applicable time points. As a control, a subgroup of participants who received Ad26.COV2.S for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after completion of the primary regimen. In addition, participants who received placebo for the primary regimen will receive placebo at 6 months, 12 months, and 24 months after

completion of the primary regimen (Table 2 and Table 3). An Ad26.COV2.S dose level of 5×10^{10} vp will be used for the booster vaccination in Cohorts 2a and 2b. If a participant in Cohort 2b does not have the second study vaccination on Day 57 (-3/+7 days), the participant will be asked to attend the Early Exit visit and will be withdrawn from the study.

Table 2: Cohort 2a Vaccination Schedule – Primary Regimen and Single Booster Vaccination

		Primary Regimen	Booster Vaccination		
Group	N	Day 1 [a] (Vac 1)	6 months [b]	12 months [b]	24 months [b]
1	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Placebo
2	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo
3	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Ad26.COV2.S 5×10^{10} vp	Placebo
4	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Ad26.COV2.S 5×10^{10} vp
5	15	Placebo	Placebo	Placebo	Placebo
Total	**135**				

a. Study vaccine will be administered as a single-dose primary regimen.
b. Study vaccine (Ad26.COV2.S or a placebo) will be administered at 6 months, 12 months, and 24 months after completion of the single-dose primary regimen.

N = number of participants; vac = vaccination; vp = virus particles.

Table 3: Cohort 2b Vaccination Schedule – Primary Regimen and Single Booster Vaccination

		Primary Regimen		Booster Vaccination		
Group	N	Day 1 [a] (Vac 1)	Day 57 [a] (Vac 2)	8 months [b]	14 months [b]	26 months [b]
1	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Placebo
2	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo
3	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Ad26.COV2.S 5×10^{10} vp	Placebo
4	30	Ad26.COV2.S 5×10^{10} vp	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Ad26.COV2.S 5×10^{10} vp
5	15	Placebo	Placebo	Placebo	Placebo	Placebo
Total	**135**					

a. Study vaccine will be administered as a 2-dose (Day 1 and Day 57) primary regimen.
b. Study vaccine (Ad26.COV2.S or a placebo) will be administered at 6 months, 12 months, and 24 months after completion of the 2-dose primary regimen. If the 2nd vaccination at Day 57 is not provided, then participants will follow the same SoA as Cohort 2a (ie, booster vaccination at 6, 12, and 24 months after completion of the single-dose primary regimen).

N = number of participants; vac = vaccination; vp = virus particles.

Study Duration

For Cohorts 1 and 3, the study duration from screening until the last follow-up visit will be approximately 15 months per participant. For these cohorts, the study consists of a screening

period of up to 28 days, vaccinations on Day 1 and Day 57, and follow-up visits up to 12 months after the second vaccination (Target Visit Day 422±21 days).

For Cohort 2a, the study duration from screening until the last follow-up visit will be approximately 36 months per participant. In this case, the study would consist of a screening period of up to 28 days, vaccination on Day 1, a single booster vaccination at 6 months, 12 months, or 24 months after completion of the single-dose primary regimen on Day 1, and follow-up visits up to 36 months after completion of the primary regimen on Day 1 (Target Visit Day 1,096±21 days).

For Cohort 2b, the study duration from screening until the last follow-up visit will be approximately 38 months per participant. In this case, the study would consist of a screening period of up to 28 days, vaccinations on Day 1 and Day 57, a single booster vaccination at 6 months, 12 months, or 24 months after completion of the 2-dose primary regimen on Day 57, and follow-up visits up to 36 months after completion of the primary regimen on Day 57 (Target Visit Day 1,152±21 days). If the 2nd vaccination at Day 57 is not provided, then participants will follow the same SoA as Cohort 2a (ie, booster vaccination at 6, 12, and 24 months after completion of the single-dose primary regimen).

For each cohort, if a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted.

Enrollment of Seropositive Participants

For all participants, a serological test will be performed at screening to detect SARS-CoV-2-specific antibodies.

In Cohort 1a and 3, the first 15 participants to be randomized will be seronegative participants. A maximum of 25 seropositive participants will be enrolled among the remaining participants in Cohorts 1a and 3. No seropositive participants will be enrolled in Cohort 1b. A maximum of 25 seropositive participants will be enrolled in Cohort 2.

Enrollment of seropositive participants in the present study will allow an evaluation of vaccine safety in this participant group.

Study Procedures

For each cohort, safety will be assessed by collection of solicited local (at injection site) and systemic AEs, unsolicited AEs, and SAEs. Other safety assessments include vital signs measurements (heart rate, supine systolic and diastolic blood pressure, respiratory rate, and body temperature) and physical examinations at the time points indicated in Section 1.3, Schedule of Activities.

After each vaccination, participants will remain under observation at the study site for at least 1 hour for the presence of any acute reactions and solicited events. Any solicited local or systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period. In addition, participants will record solicited events signs and symptoms in a diary for 7 days post-vaccination.

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. See Section 8.1.2.1 for the prespecified criteria for suspected COVID-19. If a participant experiences COVID-19-like symptoms, the following should take place:

- Participants should contact the study site at the time of symptom onset.
- A nasal swab should be collected by a health care professional from the participant at home (using available material for home swabs) or at the study site as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms and stored appropriately. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by molecular testing using the nasal swab sample.
- Participants should complete the Symptoms of Infection with Coronavirus-19 (SIC [see Section 10.7, Appendix 7, Symptoms of Infection with Coronavirus-19 (SIC)]) and record their highest body temperature daily starting on the first day they experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.
- For participants with a positive test result for SARS-CoV-2 infection, a study visit will be conducted 28 days after symptom onset to assess the clinical course of the infection, record concomitant medications since symptom onset, and obtain a blood sample for evaluation of the immune response and other biomarkers.

Further details are provided in Section 8.1.2, Procedures in Case of COVID-19-like Signs and Symptoms.

4.2. Scientific Rationale for Study Design

Vector Selection

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

Dose Selection

The rationale behind the selection of the doses is described in Section 4.3, Justification for Dose.

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.

Biomarker Collection

For participants with a positive test result for SARS-CoV-2 infection, biomarker analysis (PAXgene, RNA-seq) will be performed for evaluation of COVID-19 cases and to explore potentially informative biomarkers, eg, those associated with severe 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 benefit from participation in the study, except for compensation for the time and inconveniences that may arise from participation in the study. See Section 2.3, Benefit-Risk Assessment for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

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,[43,44] as well as the Belgian Red Cross guidelines of 450-470 mL up to 4 times a year with at least 2 months between each donation.[6]

4.3. Justification for Dose

The dose levels of Ad26.COV2.S to be assessed in the present study (5×10^{10} vp and 1×10^{11} vp) are 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). These 2 dose levels have 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, Risks Related to Study Participation.

Dose-ranging studies in immunologically naïve participants in the sponsor's HIV and Ebola programs have shown lower humoral immune responses below 5×10^{10} vp after a single vaccination. The dose level of 1×10^{11} vp is the highest dose level tested in clinical studies to date.

Therefore, both the 5×10^{10} vp and 1×10^{11} vp dose levels will be assessed to provide a safety margin and to determine whether Ad26.COV2.S has a similar immunogenicity profile to that observed with other Ad26-based vaccines.

The Ad26.COV2.S dose level for Cohort 2a has been adjusted to mimic the dosing regimen to be evaluated in study VAC31518COV3001. As a result, Cohort 2 will assess the 5×10^{10} vp dose level in a 1- and 2- dose regimen. Based on the current platform data with Ad26-based vaccines, these two regimens provide the best possibility of having an efficacious 1-dose vaccine with longevity for at least 6 months, or a 2-dose vaccine with protection after one dose if the virus is quite sensitive to neutralizing antibody and a potential increased induction of immunologic memory following the second immunization that might yield protection independent of the level of antibody at the time of encounter of the virus.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the 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

For Cohorts 1 and 3, a participant will be considered to have completed the study if he or she has completed assessments at Day 422; participants who prematurely discontinue study vaccine for any reason before completion of Day 422 will not be considered to have completed the study.

For Cohort 2, a participant will be considered to have completed the study if he or she has completed assessments at 12 months after completion of the last booster vaccination for any group. Participants who prematurely discontinue study vaccine for any reason before that time will not be considered to have completed the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before the first study vaccination. Eligibility will be reassessed pre-vaccination on Day 1.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

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

1. Participant must sign an ICF indicating that he or she understands the purpose, procedures, and potential risks and benefits of the study, and is willing to participate in the study.
2. Participant is willing and able to adhere to the prohibitions and restrictions specified in this protocol.
3. Criterion modified per Amendment 2:
   - 3.1. Applicable to Cohorts 1 and 2 only: Participant is male or female and 18 to 55 years of age, inclusive, on the day of signing the ICF.

     Applicable to Cohort 3 only: Participant is male or female and 65 years of age or older on the day of signing the ICF. For study sites in Belgium, participant is 65 to 75 years of age, inclusive, on the day of signing the ICF.
4. Criterion modified per Amendment 1:
   - 4.1. Criterion modified per Amendment 3:
   - 4.2. Criterion modified per Amendment 4:
   - 4.3. Participant must have a body mass index (BMI) <30.0 kg/m^2.
5. Criterion modified per Amendment 1:
   - 5.1. Criterion modified per Amendment 3:
   - 5.2. Criterion modified per Amendment 4:
   - 5.3. Criterion modified per Amendment 5:
   - 5.4. Criterion modified per Amendment 6:
   - 5.5. Applicable to Cohorts 1 and 2 only: Participant must be healthy, in the investigator's clinical judgment, as confirmed by medical history, physical examination, clinical laboratory assessments, and vital signs performed at screening, and must not have comorbidities related to an increased risk of severe COVID-19.[8]

     Applicable to Cohort 3 only: In the investigator's clinical judgment, participant must be either in good or stable health. Participants may have underlying illnesses such as hyperlipoproteinemia or hypothyroidism, as long as their symptoms and signs are medically controlled and not considered to be comorbidities related to an increased risk

of severe COVID-19[a].[8] If they 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 physical examination, clinical laboratory assessments, medical history, and vital signs[b].

6. Applicable to Cohorts 1 and 2 only: Contraceptive (birth control) use by women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

   Before randomization, participants who were born female must be either (as defined in Section 10.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information):

   a. Not of childbearing potential

   b. Of childbearing potential and practicing a highly effective method of contraception and agrees to remain on such a method of contraception from signing the informed consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first vaccination. Highly 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 (IUD);

      3) intrauterine hormone-releasing system (IUS);

      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 signing the informed consent until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Participants may have hypertension of mild severity (according to the Toxicity Grading Scale in Section 10.6, Appendix 6), as long as it is stable and medically controlled as defined by no change in medication over the past 6 months (except for issues of tolerability or use of similar drug with same mechanism of action, eg, thiazides, Beta blockers, Alpha blockers at the same effective dose).

[b] Participants can be enrolled with Grade 1 or Grade 2 values for vital signs measurements except for high blood pressure which is only allowed at Grade 1.

Applicable to Cohort 3 only: Before randomization, a woman must be (as defined in Section 10.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information):

a. postmenopausal (postmenopausal state is defined as no menses for 12 months without an alternative medical cause) or permanently sterile; and

b. not intending to conceive by any methods.

7. All female 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 immediately prior to each study vaccine administration.

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

9. Participant must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

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 first dose of study vaccine; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.

2. Participant has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).

3. Criterion modified per Amendment 3:

   3.1. 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).

4. Criterion modified per Amendment 3:

   4.1. Participant has abnormal function of the immune system resulting from:

   a. Clinical conditions (eg, autoimmune disease, other immune-mediated inflammatory disorders, or known or suspected immunodeficiency) expected to have an impact on the immune response or safety of the study vaccine. Participants with clinical conditions stable under treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator.

   b. Chronic (>10 days) or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study.
   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.

5. Criterion modified per Amendment 3:

   5.1. Participant has a history of any neurological disorders or seizures including Guillain-Barré syndrome, with the exception of febrile seizures during childhood.

6. Participant has a history of chronic urticaria (recurrent hives), eczema or adult atopic dermatitis.

7. Criterion modified per Amendment 3:

   7.1. Participant received treatment with immunoglobulins (Ig) in the 3 months or blood products in the 4 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.

8. Participant received or plans to receive:

   a. Licensed live attenuated vaccines - within 28 days before or after planned administration of the first or subsequent study vaccinations

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

9. Criterion modified per Amendment 1:

   9.1. Participant received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study, including receipt of any investigational agent for prophylaxis of COVID-19. Note: Participation in an observational clinical study is allowed at the investigator's discretion; please notify the sponsor (or medical monitor) of this decision.

10. Participant is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study vaccine.

11. Criterion modified per Amendment 3:

    11.1. Participant has a history of an underlying clinically significant acute or chronic medical condition, laboratory finding 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.

12. Participant had major surgery, per the investigator's judgment, within 12 weeks before vaccination, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to participate in the study or within 6 months after the last dose of study vaccine administration.

13. Participant has a contraindication to IM injections and blood draws eg, bleeding disorders.

14. Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.

15. Participant has chronic active hepatitis B or hepatitis C infection per medical history.

16. Participant has HIV infection per medical history.

17. 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.
18. Participant cannot communicate reliably with the investigator.
19. 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.
20. Participant previously received a coronavirus vaccine.
21. Criterion modified per Amendment 3:

    21.1. Participant has a positive diagnostic test result for SARS-CoV-2 infection, confirmed by PCR, at screening.
22. Criterion modified per Amendment 3:

    22.1. Based on a serological test at screening:
    Applicable to Cohorts 1a, 2, and 3 only: after a limited number of seropositive participants have been enrolled, further seropositive participants will be excluded (see Section 4.1, Overall Design).
    Applicable to Cohort 1a and 3 (first 15 participants of each cohort) and Cohort 1b only: seropositive participants will be excluded.
23. Criterion added per Amendment 1:

    23.1. Criterion modified per Amendment 3:

    23.2. Criterion modified per Amendment 4:

    23.3. Criterion modified per Amendment 5:

    23.4. Criterion modified per Amendment 6:

    Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19[a], 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, 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 (BMI $\geq$30 kg/m^2); chronic kidney disease being treated with dialysis; participants who are immunocompromised (as outlined in other exclusion criteria); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); smoking; and participants who live in nursing homes or long-term care facilities. Investigators must refer to the complete list of conditions that increase the risk of progression to severe COVID-19 available at the CDC website.[8]

    Applicable to Cohort 3 only: Participants may have hypertension of mild severity (according to the Toxicity Grading Scale in Section 10.6, Appendix 6), as long as it is stable and medically controlled as defined by no change in medication over the past

[a]The study will remain consistent with any new information, as indicated by the US CDC.

6 months (except for issues of tolerability or use of similar drug with same mechanism of action, eg, thiazides, Beta blockers, Alpha blockers at the same effective dose).

24. Criterion added per Amendment 1:

    24.1. Criterion modified per Amendment 3:

    Applicable to Cohorts 1 and 3 only: Participant currently working in an occupation with a high risk of exposure to SARS-CoV-2 (eg, health care worker or emergency response personnel) or considered at the investigator's discretion to be at increased risk to acquire COVID-19 for any other reason.

25. Criterion added per Amendment 3:

    History of confirmed COVID-19 or known exposure to an individual with confirmed COVID-19 or SARS-CoV-2 infection within the past 2 weeks (Not applicable for the seropositive participants).

26. Criterion added per Amendment 3:

    History of confirmed SARS or MERS.

NOTE: Investigators should ensure that all study enrollment criteria have been met prior to the first dose. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of 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. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Prestudy and Concomitant Therapy 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.

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. 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.

An individual who does not meet the criteria for participation in this study (screen failure) may be rescreened on one occasion only. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart 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.

If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for one of the subsequent vaccinations, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in Section 8, Study Assessments and Procedures).

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

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1. Study Vaccinations Administered

Ad26.COV2.S will be supplied at a concentration of $1x10^{11}$ vp/mL as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer will be supplied as 15 mM citrate, 5% (w/w) hydroxypropyl-β-cyclodextrin, 0.4% (w/w) ethanol, 0.03% (w/w) polysorbate 80, 75 mM NaCl, pH 6.2 and placebo is 0.9% NaCl.

For blinding purposes, the same volume (1 mL) will be administered to all participants in a cohort.

Study vaccine will be administered by IM injection into the deltoid muscle, preferably of the non-dominant arm:

- Ad26.COV2.S:
  - $5x10^{10}$ vp: 0.75 mL of formulation buffer is withdrawn from one vial and added to a vial containing 0.75 mL $1×10^{11}$ vp/mL, providing $5x10^{10}$ vp/mL in a vial with an extractable volume of more than 1 mL. Then 1 mL will be withdrawn from this vial.
  - $1x10^{11}$ vp: 2 single-use vials (0.5 mL will be withdrawn from 1 vial and added to a second vial, which will then have an extractable volume of more than 1 mL. Then, 1 mL will be withdrawn from the second vial).

- Placebo: 0.9% NaCl solution: 1 mL

Study vaccine administration must be captured in the source documents and the electronic case report form (eCRF).

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

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 site investigational product and procedures manual (SIPPM) and the Investigational Product Preparation Instructions (IPPI) for additional guidance on study vaccine preparation, handling, and storage.

An unblinded pharmacist or other qualified individual who will have no other study function will prepare the appropriate vial and syringe, labeled with the participant's identification number, and provide the syringe to the blinded vaccine administrator 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 study 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 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 vaccines are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Vaccine Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Within each cohort, participants will be randomly assigned to 1 of the vaccine groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. For Cohort 2, participants will be first randomly assigned to either Cohort 2a or 2b, and subsequently randomly assigned to 1 of the 5 vaccine groups in each of Cohort 2a and 2b (see Table 2 and Table 3). Randomization will be balanced by using randomly permuted blocks. For Cohorts 1 and 3, randomization will be stratified by study site and seropositivity status at screening. For Cohort 2, randomization will be stratified study site, seropositivity status at screening, and age group (60% of participants ≥18 to ≤40 years and 40% of participants aged >40 to ≤55 years).

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit 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.

If, due to the urgency of study initiation during the ongoing pandemic, the IWRS is not yet available at the planned time of randomization of the first participant, randomization may be started based on a paper randomization list until the IWRS is live.

Blinding

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 intervention 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 (DBL) and unblinding.

Under normal circumstances, the blind should not be broken until the database is finalized. 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.

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. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis. Refer to Section 9.5, Planned Analysis, for details of the analyses.

If randomized participants are withdrawn from vaccination before the first dose of study vaccine is administered, additional participants may be recruited to replace these participants at the discretion of the sponsor. Any replacement participant will be assigned to the same group as the original (discontinued) participant. If randomized participants are withdrawn after the first dose of study vaccine is administered, they will not be replaced.

In the event that randomization is started based on a paper randomization list, sealed randomization codes will be provided for each participant containing coded details of study vaccine allocation. All randomization codes, whether opened or sealed, will be collected after the end of the participant's participation in the study. If emergency unblinding is required, the investigator may determine the identity of the study vaccine by opening the sealed code. The date, time, and reason for the unblinding must be documented in the appropriate section of the eCRF, and in the source document.

6.4. Study Vaccine Compliance

Study vaccines will be administered IM by blinded qualified study-site personnel at the study site. Details of each administration will be recorded in the eCRF (including date and time of injection and deltoid used for injection). For blinding procedures, see Section 6.3, Measures to Minimize Bias: Randomization and Blinding.

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

There will be no study vaccination after the end of the study.

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 an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AEs/SAEs: (ie, the participant will remain at the study site for at least 1 hour and will be closely monitored for allergic or other reaction 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 eCRF.
- Report as a special reporting situation.

6.8. Prestudy and Concomitant Therapy

Prestudy specific therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations administered up to 30 days before first dose of study vaccine must be recorded at screening.

Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outline in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

Use of any experimental medication (including experimental vaccines other than the study vaccine) will lead to discontinuation of administration of any subsequent study vaccination. Any participant who has been given an anti-COVID-19 vaccine or treatment will not receive further study vaccination. Participants may not receive an investigational drug or use an invasive investigational medical device within 30 days or receive an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine.

Vaccination with licensed live attenuated vaccines within 28 days of a study vaccination (ie, before or after) is prohibited. Other licensed (not live) vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) 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.

Analgesic medications and nonsteroidal anti-inflammatory drugs may be used post-vaccination at the first signs of symptoms or in case of medical need. Use of these medications as routine prophylaxis prior to study vaccine administration is prohibited.

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.

Chronic (>10 days) or recurrent use of systemic corticosteroids[a], and administration of antineoplastic and immunomodulating agents or radiotherapy is prohibited during the study and within 6 months before the planned administration of the first dose of 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, Exclusion Criteria 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 medication will not be included in the immunogenicity analyses.

6.9. Study Vaccination Pausing Rules

For Cohorts 1a and 3, randomization and vaccination of participants will be suspended during review of the 24-hour data following the first administration of study vaccine to 5 sentinel participants and, if applicable, during the review of safety data after the first 15 participants have received the first vaccination (see Section 4.1, Overall Design).

For each cohort, the PI and the SRP will monitor safety in a blinded manner, including the study vaccination pausing rules. If a study vaccination is considered to raise significant safety concerns (and a specific set of pausing criteria have been met), further vaccination of participants will be paused. The concerned data will be reviewed by the DRC, after which the DRC will recommend whether the pause can be lifted or not, or whether other steps are needed.

The DRC will review blinded data first but has the right to request the randomization codes and review unblinded data if deemed necessary. The DRC will make recommendations regarding the continuation of the study to the sponsor study team. The sponsor study team will communicate conclusions regarding study continuation to the investigator, the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), and applicable health authorities as appropriate.

After the first DRC meeting triggered by the occurrence of a given pausing rule, the DRC will convene thereafter for each additional participant meeting that pausing rule.

The occurrence of any of the following events 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

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

Note: All cases of death will be sent for DRC information. Upon their review, the DRC may then decide whether a study pause is required.

2. One or more participants experience an SAE or a Grade 4 (solicited or unsolicited) AE or a persistent (upon repeat testing) Grade 4 laboratory abnormality 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; OR
4. Three or more participants experience a Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor), that is determined to be related to study vaccine; OR
5. Three or more participants experience a persistent (upon repeat testing) Grade 3 laboratory abnormality related to the same laboratory parameter and considered related to study vaccine; OR
6. Three or more participants experience a Grade 3 solicited AE of the same type, determined to be related to study vaccine, and persisting as Grade 3 for longer than 3 consecutive days[a].

For number 2 and number 5: to assess abnormal laboratory values, the test must be repeated at least once, within 48 hours of the site becoming aware of the abnormal value.

For number 4, number 5, and number 6: after each DRC review of similar AEs, the Committee will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

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 SAE form to Global Medical Safety Operations, if applicable), immediately and no later than 24 hours after becoming aware of any related AE of Grade 3 or above AND update the eCRF with relevant information on the same day the AE information is collected. A thorough analysis of all Grade 3 (or above) cases will be carried out by the sponsor's medical monitor or designee, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted. All sites will be notified immediately in case of a study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of DRC members and coordination of a DRC meeting in case of a study pause.

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 DRC 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.

[a] The day of occurrence of the AE is counted as Day 1.

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

Resumption of vaccinations will start only upon receipt of written recommendations by the DRC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. These communications from the DRC 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

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

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

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic (>10 days) or recurrent use of systemic corticosteroids and administration of antineoplastic and immunomodulating agents or radiotherapy
- Withdrawal of consent
- Participant has a positive test result for SARS-CoV-2 infection during the study (see Section 8.1.2)
- Participant receives any experimental medication (including experimental vaccines other than the study vaccine) or receives an anti-COVID-19 vaccine or treatment.

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
- Participant in Cohort 2b does not have the second study vaccination on Day 57 (-3/+7 days)

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, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). 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

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 Schedule of Activities summarizes the frequency and timing of safety, reactogenicity, immunogenicity and other measurements applicable to each cohort in this study. See Section 1.3 for details.

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. Actual dates and times of assessments will be recorded in the source document and in the eCRF.

Participants will be provided a thermometer (to measure body temperature), ruler (to measure local injection site reactions), and participant diary to record body temperature and solicited local (at injection site) and systemic signs and symptoms. The 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 diary will be reviewed by the study personnel at visits indicated in the Section 1.3, Schedule of Activities. If the diary review is missed, the diary will be reviewed during the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be completed.

Participants will also be provided with a booklet (to answer a daily signs and symptoms surveillance question, and including the SIC) and a kit to collect nasal swabs if they experience COVID-19-like symptoms during the study (see Section 8.1.2, Procedures in Case of COVID-19-like Signs and Symptoms and Section 8.1.2.1, Prespecified Criteria for Suspected COVID-19).

For participants who do not undergo additional procedures due to COVID-19-like signs and symptoms, the maximum amount of blood drawn in this study will not exceed approximately 785 mL for Cohorts 1a or 3, 1,045 mL for Cohort 1b, 653 mL for Cohort 2a and 890.5 mL for Cohort 2b. For participants who undergo additional procedures due to COVID-19-like signs and symptoms, an additional 17.5 mL of blood will be collected. Refer to Section 1.3, Schedule of Activities for the total blood volume (serum and, as applicable, PBMCs and whole blood samples) to be collected at each visit and over the complete course of the study for each cohort and in case of COVID-19-like signs and symptoms. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Study visits, other than screening and visits at which study vaccination is scheduled, may take place at the participant's home if there are travel restrictions in case of an ongoing pandemic.

Visit Windows

Visit windows that will be allowed are summarized below. 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. If a participant misses a vaccination, the post-vaccination visits will be calculated from the imputative vaccination date according to protocol.

Table 4: Visit Windows Cohort 1a

Visit	Target Visit Day	Allowed Window	Primary Purpose
5 [a]	8	±2 days	7 days post-vaccination 1 safety visit
6	15	±3 days	14 days post-vaccination 1 safety and immunogenicity visit
7	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
8	57	-3/+7 days	Vaccination 2
10 [a]	64 [b]	±2 days	7 days post-vaccination 2 safety visit
11	71 [b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
12	85 [b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
13	239 [b]	±21 days	6 months post-vaccination 2 safety and immunogenicity visit
14	422	±21 days	12 months post-vaccination 2 safety and immunogenicity visit

a. If a participant comes in early for Visit 5 or 10, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will then be returned by the participant at the next visit. If an event is still ongoing on the Target Visit Day, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

b. The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

Table 5: Visit Windows Cohort 1b

Visit	Target Visit Day	Allowed Window	Primary Purpose
4 [a]	8	±2 days	7 days post-vaccination 1 safety and immunogenicity visit
5	15	±3 days	14 days post-vaccination 1 safety and immunogenicity visit
6	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
7	57	-3/+7 days	Vaccination 2
9 [a]	64 [b]	±2 days	7 days post-vaccination 2 safety and immunogenicity visit
10	71 [b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
11	85 [b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
12	239 [b]	±21 days	6 months post-vaccination 2 safety and immunogenicity visit
13	422	±21 days	12 months post-vaccination 2 safety and immunogenicity visit

a. If a participant comes in early for Visit 4 or 9, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will then be returned by the participant at the next visit. If an event is still ongoing on the Target Visit Day, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

b. The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

Table 6: Visit Windows Cohort 2a

Visit	Target Visit Day	Allowed Window	Primary Purpose
3 [a]	8	±2 days	Safety and immunogenicity visit 7 days after primary regimen
4	29	±3 days	Safety and immunogenicity visit 28 days after primary regimen
5	183	±21 days	Safety and immunogenicity visit / single booster vaccination 6 months after primary regimen [c]
6 [a]	190 [b]	±2 days	Safety and immunogenicity visit 7 days post-booster vaccination
7	211 [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
8	366	±21 days	Safety and immunogenicity visit / single booster vaccination 12 months after primary regimen [c]
9 [a]	373 [b]	±2 days	Safety and immunogenicity visit 7 days post-booster vaccination
10	394 [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
11	731	±21 days	Safety and immunogenicity visit / single booster vaccination 24 months after primary regimen [c]
12 [a]	738 [b]	±2 days	Safety and immunogenicity visit 7 days post-booster vaccination
13	759 [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
14	913 [b]	±21 days	Safety and immunogenicity visit 6 months post-booster vaccination
15	1,096 [b]	±21 days	Safety and immunogenicity visit 12 months post-booster vaccination

a. If a participant comes in early for Visit 3, 6, 9, or 12, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit. If an event is still ongoing on the Target Visit Day, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

b. The timings of visits after a booster vaccination will be determined relative to the actual day of that vaccination.

c. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the single-dose primary regimen and will receive placebo at the other indicated time points. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

Table 7: Visit Windows Cohort 2b

Visit	Target Visit Day	Allowed Window	Primary Purpose
3 [a]	8	±2 days	Safety and immunogenicity visit 7 days post-vaccination 1
4	29	±3 days	Safety and immunogenicity visit 28 days post-vaccination 1
5	57	-3/+7 days	Vaccination 2
6 [a]	64 [b]	±2 days	Safety and immunogenicity visit 7 after primary regimen
7	85 [b]	±3 days	Safety and immunogenicity visit 28 after primary regimen
8	239 [b]	±21 days	Safety and immunogenicity visit / single booster vaccination 6 months after primary regimen [c]
9 [a]	246 [b]	±2 days	Safety and immunogenicity visit 7 days post-booster vaccination
10	267 [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
11	422 [b]	±21 days	Safety and immunogenicity visit / single booster vaccination 12 months after primary regimen [c]
12 [a]	429 [b]	±2 days	Safety and immunogenicity visit 7 days post-booster vaccination
13	450 [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
14	787 [b]	±21 days	Safety and immunogenicity visit / single booster vaccination 24 months after completion of primary regimen [c]
15 [a]	794 [b]	±2 days	Safety and immunogenicity visit 7 days post-booster vaccination
16	815 [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
17	969 [b]	±21 days	Safety and immunogenicity visit 6 months post-booster vaccination
18	1,152 [b]	±21 days	Safety and immunogenicity visit 12 months post-booster vaccination

a. If a participant comes in early for Visit 3, 6, 9, 12, or 15, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will be returned by the participant at the next visit. If an event is still ongoing on the Target Visit Day, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

b. The timings of visits after the second vaccination or a booster vaccination will be determined relative to the actual day of that vaccination.

c. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 6 months, 12 months, or 24 months after completion of the 2-dose primary regimen and will receive placebo at the other indicated time points. If the 2nd vaccination at Day 57 is not provided, then participants will follow the same SoA as Cohort 2a (ie, booster vaccination at 6, 12, and 24 months after completion of the single-dose primary regimen). Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 3 for further details.

Table 8: Visit Windows Cohort 3

Visit	Target Visit Day	Allowed Window	Primary Purpose
4 [a]	8	±2 days	7 days post-vaccination 1 safety visit
5	15	±3 days	14 days post-vaccination 1 safety and immunogenicity visit
6	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
7	57	-3/+7 days	Vaccination 2
9 [a]	64 [b]	±2 days	7 days post-vaccination 2 safety visit
10	71 [b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
11	85 [b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
12	239 [b]	±21 days	6 months post-vaccination 2 safety and immunogenicity visit
13	422	±21 days	12 months post-vaccination 2 safety and immunogenicity visit

a. If a participant comes in early for Visit 4 or 9, ie, 1 or 2 days prior to the Target Visit Day per the allowed visit window, a subsequent phone call will be made at the end of the diary period to collect diary information recorded between the actual visit and the end of the diary period. The diary will then be returned by the participant at the next visit. If an event is still ongoing on the Target Visit Day, the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.

b. The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

Screening

Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 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 4 weeks prior to first 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 molecular test for the presence of SARS-CoV-2 infection must be done within 4 days before vaccination. The study-specific ICF date will be entered into the eCRF. 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 Section 1.3, Schedule 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)
- Pharmacy manual/SIPPM
- IWRS Manual
- Sample ICF
- Laboratory manual
- Participant diaries
- Nasal swab kits
- Participant instructions and booklet: COVID-19-like signs and symptoms daily surveillance, nasal swab instructions, and SIC (for daily completion, if symptomatic)
- Contact information page(s)
- eCRF completion guidelines

8.1. Immunogenicity and Efficacy Assessments

8.1.1. Immunogenicity Assessments

Venous blood samples will be collected for assessment of humoral or cellular immune responses. Sample volumes and time points are detailed in the Schedule of Activities for Cohort 1a (Section 1.3.1), Cohort 1b (Section 1.3.2), Cohort 2a (Section 1.3.3), Cohort 2b (Section 1.3.4) and Cohort 3 (Section 1.3.5), and for participants with a positive test result for SARS-CoV-2 infection (Section 1.3.6).

If the participant is unable to complete the study without withdrawing consent, immunogenicity samples will be taken at the early exit visit, but only if the early exit visit is at least 10 days after the previous immunology blood draw. See Section 1.3, Schedule of Activities for further details.

Humoral and cellular immunogenicity assays may include, but are not limited to, the assays summarized in Table 9 and Table 10, respectively.

Table 9: Summary of Humoral Immunogenicity Assays

Assay	Purpose
Secondary endpoints	
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 (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S protein
Exploratory endpoints	
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other strain), as measured by an alternative neutralization assay (different from the VNA used for the secondary endpoint)
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein, if such an assay can be developed
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model

ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay

Table 10: Summary of Cellular Immunogenicity Assays

Assay	Purpose
Secondary endpoints	
Flow cytometry (ICS)	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by ICS including $CD4^+/CD8^+$, IFNγ, IL-2, TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers
Exploratory endpoints	
ELISpot	IFNγ and IL-4 responses to SARS-CoV-2 S protein peptides by PBMCs, based on single ELISpot
Gene expression analysis	Analysis of gene expression by RNA transcript profiling and/or analysis of protein translates, in cells or whole blood stimulated with SARS-CoV-2 S protein peptides or in unstimulated cells or whole blood (ex vivo)
Cytokine profiling (ELISA or multiplexed arrays)	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells or whole blood stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells or whole blood, by ELISA or multiplexed arrays and confirmation by functional in vitro assays
T and B cell phenotyping	Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube isolated PBMCs)

ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot (assay); ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha

8.1.2. Procedures in Case 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 Schedule of Activities in Section 1.3.6.

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. See Section 8.1.2.1 for the prespecified criteria for suspected COVID-19. Participants will also be contacted regularly by study-site personnel during the study to remind them to complete the SIC in the event of any signs and symptoms and to contact the site at the time of symptom onset.

For each cohort, if participants experience COVID-19-like symptoms, the following should take place:

- Participants should contact the study site at the time of symptom onset.
- A nasal swab should be collected by a health care professional from the participant at home (using available material for home swabs) or at the study site as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms and stored appropriately. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by molecular testing using the nasal swab sample. Leftover nasal swab samples will be stored and might be used for central laboratory confirmation and/or quantification of SARS-CoV-2 and for detection of other respiratory pathogens.
- Participants should complete the SIC (see Section 10.7, Appendix 7, Symptoms of Infection with Coronavirus-19 [SIC]) and record their highest body temperature daily starting on the first day they experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.
- For participants with a positive test result for SARS-CoV-2 infection, a study visit will be conducted 28 days after symptom onset to assess the clinical course of the infection, record concomitant medications since symptom onset, and obtain a blood sample for assessment of the humoral immune response (VNA, ELISA, and Fc functionality) and other biomarkers (RNA-seq).

If a participant has a positive test result for SARS-CoV-2 infection, the participant may be requested to remain at home and not visit the study site. If necessary, study-site personnel will visit the participant at home. 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. The participant will not receive further study vaccinations but should remain on study for follow-up with assessments of safety and immunogenicity. The participant will be followed until resolution of clinical symptoms.

If a participant has a positive test result for influenza infection, study visits will continue per the Schedule of Activities.

8.1.2.1. Prespecified Criteria for Suspected COVID-19

The criteria for suspected COVID-19 (ie, the triggers to proceed with contacting the study site and collection of the nasal swab) are prespecified as follows:

- 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)
- Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)
- Neurologic symptoms (numbness, difficulty forming or understanding speech)
- Red or bruised looking toes
- Skin rash
- New loss of taste or smell

8.1.3. Efficacy Assessments

As an exploratory objective, a preliminary analysis of vaccine efficacy in the prevention of molecularly confirmed COVID-19 will be performed. Identification and molecular confirmation of SARS-CoV-2 infection will be performed as described in Section 8.1.2, Procedures in Case of COVID 19-like Signs and Symptoms.

As an additional exploratory objective, a preliminary analysis of vaccine efficacy in the prevention of asymptomatic SARS-CoV-2 infection will be performed. A non-S protein ELISA (eg, SARS-CoV-2 N ELISA), if such an assay can be developed, will be performed to identify cases of asymptomatic infection. This assay will be performed on samples obtained at:

- Cohorts 1a, 1b, and 3: on Day 1 (pre-vaccination), at 6 months post-vaccination 2, and at 12 months post-vaccination 2
- Cohorts 2a and 2b: on Day 1 (pre-vaccination), and at 6 months and 12 months after completion of the primary regimen

8.2. Safety Assessments

Details regarding the DRC are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

AEs will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event 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 Schedule of Activities.

8.2.1. Physical Examinations

A full physical examination, including height and body weight, will be carried out at screening. To obtain the actual body weight, participants must be weighed lightly clothed. The height should be measured without footwear.

At all other visits, an abbreviated, symptom-directed examination might be performed by the investigator based on any clinically relevant issues or symptoms, and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or designated medically trained clinician. 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

Body temperature (oral route preferred, or in accordance with the local standard of care), pulse/heart rate, respiratory rate, and blood pressure will be assessed. Confirmatory vital signs measurement can be performed if inconsistent with a prior measurement.

Participants will utilize a diary to record body temperature measurements post-vaccination.

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

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

8.2.3. Pregnancy Testing

For Cohorts 1 and 2 only, a urine pregnancy test for women of childbearing potential will be performed at screening and before each vaccination.

Additional pregnancy tests may be performed, 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.

8.2.4. Clinical Laboratory Assessments

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event or medical history section of the CRF. The laboratory reports must be filed with the source documents.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, 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) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported for all participants 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 the signing of the ICF and moment of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Solicited AEs, collected through a diary, will be recorded for each vaccination from the time of vaccination until 7 days post-vaccination.

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported for all participants from the moment of first 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.

All AEs will be followed until resolution or until clinically stable.

Serious Adverse Events

All SAEs, as well as PQC, 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, 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.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event 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 a 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 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 the injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their diary.

After each vaccination, participants will remain under observation at the study site for at least 1 hour for the presence of any acute reactions and solicited events.

In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination. All participants will be provided with a diary and instructions on how to complete the diary (see Overview in Section 8, Study Assessments and Procedures). Diary information will be transferred to the sponsor. After review and verbal discussion of the initial diary entries with the participant, the investigator will complete his/her own assessment in the relevant sections of the

eCRF. Once a solicited sign or symptom from a 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 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.[24,32]

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 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 one measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[37]

Participants will also be instructed on how to note signs and symptoms in the 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, and myalgia.

Unsolicited Adverse Events

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

8.3.3. Follow-up of 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, SAE, or PQC as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study vaccination.

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

8.4. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

8.5. Biomarkers

For participants with a positive test result for SARS-CoV-2 infection, a blood sample for evaluation of biomarkers (eg, those associated with severe COVID-19) will be collected 28 days after symptom onset (see Section 1.3.6, Procedures for Participants with COVID-19-like Signs and Symptoms).

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 Statistical Analysis Plan.

9.1. Statistical Hypotheses

No formal statistical hypothesis for safety or immunogenicity will be tested.

9.2. Sample Size Determination

The number of participants chosen for this study will provide a preliminary safety and immunogenicity assessment. Placebo recipients are included for blinding and safety purposes and will provide additional control specimens for immunogenicity assays.

While mild-to-moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. When 75 and 120 participants are vaccinated, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 3.9% and <2.5% respectively. Table 11 provides the probabilities of observing at least one AE at given true AE rates.

Table 11: Probability of Observing at Least One Adverse Event Given a True Adverse Event Incidence

True Adverse Event Incidence	Probability of Observing at Least One Adverse Event	
	N=75	N=120
1%	53%	70%
2.5%	85%	95%
5%	98%	>99%
10%	>99%	>99%
20%	>99%	>99%

N: number of participants receiving study vaccine (Ad26.COV2.S or a placebo).

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

FAS: The full analysis set will include all participants with at least one vaccine administration documented.

PPI: The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural infection occurring after screening (if applicable) will be excluded from the analysis set.

PPE: The per protocol efficacy population will include all randomized participants having received at least 1 vaccination for whom efficacy data concerning endpoint measures are available. All efficacy analyses will be done according to the as treated principle (ie, actually received vaccinations).

9.4. Statistical Analyses

The Statistical Analysis Plan will be finalized prior to interim DBL 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.

9.4.1. General Considerations

Analysis populations are defined in Section 9.3, Populations for Analysis Sets. Planned analyses are defined in Section 9.5, Planned Analysis.

For safety and immunogenicity analyses, results will be analyzed by vaccine group. In addition, safety and immunogenicity analyses will be repeated by vaccine group and participant seropositivity status at screening. Immunogenicity subanalyses will also be performed by BMI, ethnicity, and other factors as will be described in the Statistical Analysis Plan.

9.4.2. Primary Endpoints

Safety Endpoints

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group. In addition, for selected tables, tabulations pooled by vaccine dose will also be provided. All safety analyses will be made on the FAS.

Adverse Events

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 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 vaccine group.

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

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The number and percentages of participants with at least one solicited local (at injection site) or systemic AE will be presented. The 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.

Clinical Laboratory Tests

Laboratory data (abnormal or graded, when available) will be listed by participant and time point.

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Physical examination findings will be summarized at baseline. A listing of the abnormalities will be made.

9.4.3. Secondary Endpoints

Immunogenicity Endpoints

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval, or median and interquartile range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters at all available time points. Graphical

representations of immunologic parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

In addition, the ratio between neutralizing and binding antibodies as determined by VNA and S protein ELISA, respectively, will be calculated.

The immunogenicity analyses will be performed on the PPI population. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols).

9.4.4. Tertiary/Exploratory Endpoint(s)

Detailed statistical methodology for analysis of exploratory endpoints will be described in the Statistical Analysis Plan.

9.4.5. Other Analyses

Descriptive analysis will be performed for the results of the SIC and results of diagnostic tests for SARS-CoV-2 infection after screening. Further details will be provided in the Statistical Analysis Plan.

Statistical analysis of biomarker responses (eg, RNA-seq responses) will be detailed in a separate Statistical Analysis Plan.

9.5. Planned Analysis

Interim and primary analyses for each cohort are presented in Figure 7.

Interim and Primary Analyses for Cohort 1a

A first interim analysis post-dose 1 for Cohort 1a is planned when approximately 375 participants have completed Day 29 (ie, 28 days after the first study vaccination) or discontinued earlier. This interim analysis will include all available safety data for approximately 375 participants through Day 29 and may include immunogenicity data (VNA, ELISA, and Th1/Th2 assay) for at least 25 seronegative participants (ie, participants who were seronegative at screening) per group through Day 15 (ie, 14 days after the first study vaccination)[a]. A second interim analysis for Cohort 1a will include immunogenicity data through Day 29 (all available VNA and ELISA data for seronegative participants; Th1/Th2 assay data for approximately 40 seronegative participants per group). For logistical reasons, aspects of the first and second interim analyses may be combined.

The first primary analysis post-dose 2 for Cohort 1a will be performed when approximately 375 participants have completed Day 85 (ie, 28 days after the second study vaccination) or discontinued earlier. The primary analysis will include all available safety data for all participants through Day 85. It may also include immunogenicity data through Day 71, ie, 14 days after the

[a] May be performed based on operational availability of data.

second study vaccination (all available VNA and ELISA data for seronegative participants; Th1/Th2 assay data for approximately 40 seronegative participants per group)[a]. A second primary analysis for Cohort 1a will include immunogenicity data through Day 85 (all available VNA and ELISA data for seronegative participants; Th1/Th2 assay data for approximately 40 seronegative participants per group). For logistical reasons, aspects of the first and second primary analyses may be combined.

Interim and Primary Analyses for Cohort 2

An interim analysis for Cohort 2 will be performed when 28-day safety data is collected for approximately 270 participants after the first study vaccination. This safety analysis may be required as the basis for enrollment of adults aged ≥18 to ≤55 years in subsequent larger studies. It will also include available immunogenicity data for seronegative participants (VNA and ELISA).

The primary analysis for Cohort 2 will include all available safety data for approximately 270 participants through 28 days after completion of the second study vaccination in the 2-dose primary regimen. It will also include available immunogenicity data for seronegative participants (VNA and ELISA).

Interim analyses of the data from each booster vaccination will be performed after the last participant receives their respective booster vaccination and will include all available safety and immunogenicity data up to 28 days after the vaccination.

Interim and Primary Analyses for Cohort 3

The analysis strategy for Cohort 3 is the same as for Cohort 1a.

A first interim analysis post-dose 1 for Cohort 3 is planned when approximately 375 participants have completed Day 29 (ie, 28 days after the first study vaccination) or discontinued earlier. This interim analysis will include all available safety data for approximately 375 participants through Day 29 and may include immunogenicity data (VNA, ELISA, and Th1/Th2 assay) for at least 25 seronegative participants per group through Day 15 (ie, 14 days after the first study vaccination)[a]. A second interim analysis for Cohort 3 will include immunogenicity data through Day 29 (all available VNA and ELISA data for seronegative participants; Th1/Th2 assay data for approximately 40 seronegative participants per group). For logistical reasons, aspects of the first and second interim analyses may be combined.

The first primary analysis post-dose 2 for Cohort 3 will be performed when approximately 375 participants have completed Day 85 (ie, 28 days after the second study vaccination) or discontinued earlier. The primary analysis will include all available safety data for all participants through Day 85. It may also include immunogenicity data through Day 71, ie, 14 days after the second study vaccination (all available VNA and ELISA data for seronegative participants;

[a] May be performed based on operational availability of data.

Th1/Th2 assay data for approximately 40 seronegative participants per group)[a]. A second primary analysis for Cohort 3 will include immunogenicity data through Day 85 (all available VNA and ELISA data for seronegative participants; Th1/Th2 assay data for approximately 40 seronegative participants per group). For logistical reasons, aspects of the first and second primary analyses may be combined.

Final Analysis of the Study

The final analysis will be performed when the last participant from Cohorts 1a and 3 completes the final visit (12 months after second study vaccination) or discontinues earlier. It will include any data for Cohorts 1a and 3 that were not available for the interim and primary analyses and all data that are available for Cohorts 1b and 2 (including any data after booster vaccination). It will also include data from participants in each cohort who were seropositive for SARS-CoV-2-specific antibodies at screening.

End-of-study Analysis

The end-of-study analysis will be performed when all included participants have completed the last visit or last booster vaccination follow-up visit or discontinued earlier.

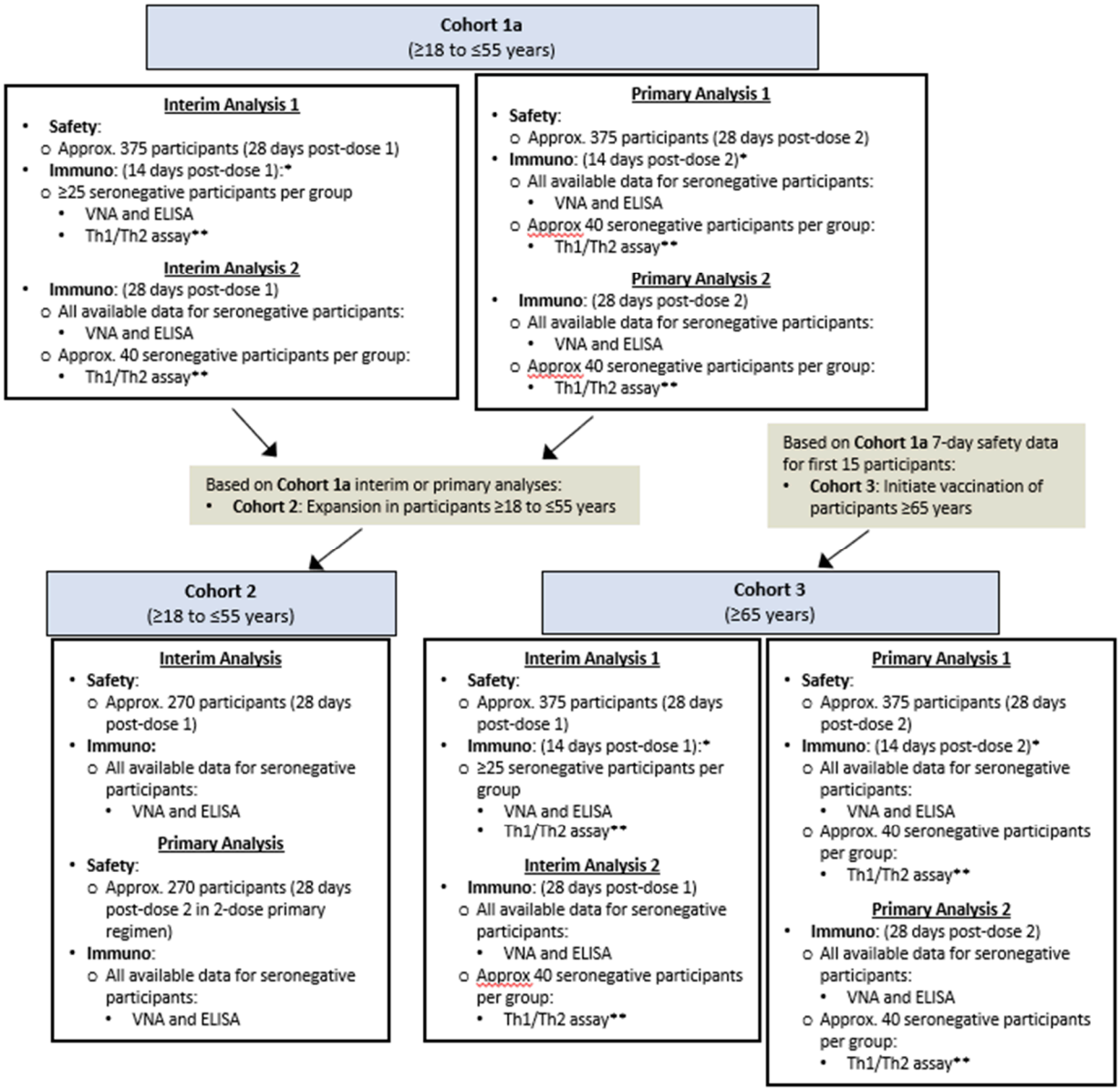
For all analyses, all data available at the time of the analysis will be included. If any of the above-mentioned analyses coincide, the analyses will be combined. Additional interim analyses may be performed for safety and/or immunogenicity to facilitate decision making with regards to the planning of future studies.

Selected available group unblinded immunogenicity data and blinded safety data from the interim analysis of Cohorts 1a, 1b, and 3 will be published. Following the 7-day post-vaccination 2 safety data being available in Cohorts 1a, 1b, and 3, selected available group unblinded immunogenicity and group unblinded safety data will be published. Participants, clinical staff, and study-site personnel will remain blinded to the study vaccine allocation until the end of study.

Selected members of the statistical programming and the statistics group will receive individual level unblinded data pertaining to study VAC31518COV1001 when unblinding at the participant level is required. In addition, they 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 (see Statistical Analysis Plan). They will inform the DRC 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 DRC will be described in the Statistical Analysis Plan.

The Statistical Analysis Plan will describe the planned analyses in greater detail.

Figure 7: Interim and Primary Analyses



*May be performed based on operational availability of data.
**Analysis of VNA/ELISA may be performed before availability of Th1/Th2 data, which may not be available at the time of this analysis.
ELISA = enzyme-linked immunosorbent assay; Th = T-helper; VNA = virus neutralization assay

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	adenovirus type 26
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AdVac®	adenoviral vaccine
AE	adverse event
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
Cont	continuous
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CT	computed tomographic
d	day(s)
DBL	database lock
DNA	deoxyribonucleic acid
DRC	Data Review Committee
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ERD	enhanced respiratory disease
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	intracellular staining
IEC	Independent Ethics Committee
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IM	intramuscular(ly)
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
mo	month(s)
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPE	per protocol efficacy
PPI	per protocol immunogenicity
PQC	product quality complaint
RNA	ribonucleic acid

RSV	respiratory syncytial virus
RT-PCR	reverse-transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SIC	Symptoms of Infection with Coronavirus-19
SIPPM	site investigational product and procedures manual
SoA	Schedule of Activities
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
tel	telephone contact
Th	T-helper
TNFα	tumor necrosis factor alpha
vac	vaccination
VNA	virus neutralization assay
vp	virus particles
WHO	World Health Organization

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local laboratory:

Protocol-Required Clinical Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Hemoglobin</td><td>Prothrombin time
Activated partial thromboplastin time</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="3">Sodium
Potassium
Blood urea nitrogen (BUN)
Creatinine
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Glucose
Protein
Blood</td><td><u>Sediment (if dipstick result is abnormal)</u></td></tr>
<tr><td colspan="3">If dipstick result is abnormal, microscopy will be used to measure sediment.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Urine Pregnancy Testing (for women of childbearing potential only).</td></tr>
</table>

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 Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP 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 PI
- 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 PI, 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, Study-Specific Ethical Design Considerations.

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

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. 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 date and sign the ICF 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 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 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, Withdrawal From the Use of Research Samples).

10.3.6. Committees Structure

Data Review Committee

An internal DRC, consisting of members that are not directly involved in the study conduct, data management, or statistical analysis, will be established and will monitor data to ensure the continuing safety of the participants enrolled in this study. The DRC will review data as indicated in Section 4.1, Overall Design. When appropriate, the conclusions of the DRC will be communicated to the investigators, the IRB/IEC, and the national regulatory authorities.

In addition, ad hoc review may be performed further to the occurrence of any AE/SAE leading to a study pausing situation as outlined in Section 6.9, Study Vaccination Pausing Rules, or at request of the sponsor's medical monitor or designee. The PI(s) and SRP will inform the DRC of any AE of concern.

The DRC will review blinded data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

It will also be possible for the DRC to review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions. If this is the case, a biomarker representative (not involved in the conduct of the study) will be part of the DRC.

This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DRC responsibilities, authorities, and procedures will be documented in its 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, including exploratory biomarker research 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 exploratory biomarker 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 on-site 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 (CRFs) are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. 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 medication; vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Participant- and investigator-completed scales and assessments designated by the sponsor (ie, diary to record solicited AEs, daily signs and symptoms surveillance question, and SIC) will be recorded and will be considered source data. The participant's 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 eCRF 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. 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 source documents, 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, 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.

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 any 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, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

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 judgment 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 one 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 serious and unexpected suspected adverse reaction 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,[42] included in Section 10.6, Appendix 6, Toxicity Grading Scale.

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

The severity of solicited signs and symptoms will be graded in the diary by the participant based on the severity assessment provided in the diary and then verified by the investigator using the toxicity grading scale in Section 10.6, Appendix 6. (Note: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever]).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- 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 intervention from breast-feeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page 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 an SAE.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (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, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 one 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 a highly effective method of contraception, as described throughout the inclusion criteria.

10.6. Appendix 6: 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).

A: Tables for Clinical Abnormalities

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 judgment 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	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

B: Tables for Laboratory Abnormalities

Laboratory tests may be performed during routine medical care and assessment of AEs or other medical events based on the investigator's judgment.

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** ULN is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

10.7. Appendix 7: Symptoms of Infection with Coronavirus-19 (SIC)

Note: An example SIC is provided below. Participants will be provided with the most recent version of the 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 this **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

In the last 24 hours, have you experienced…	**Please rate the severity of each symptom you experienced.**
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
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

In the last 24 hours, have you experienced…	**Please rate the severity of each symptom you experienced.**
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
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

In the last 24 hours, have you experienced…	**Please rate the severity of each symptom you experienced.**
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** ☐ **other**

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**

10.8. Appendix 8: Case Definitions for COVID-19

10.8.1. Case Definition for Moderate to Severe COVID-19

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.
** 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

[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).

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.
- 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

10.8.2. 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 10.8.1.

10.8.3. US FDA Harmonized Case Definition for COVID-19

The following case definition is recommended by the FDA as a primary or secondary endpoint for all efficacy studies against COVID-19:

If a participant presents with symptoms as those listed by the US FDA harmonized case definition[10] (see Section 10.9, Appendix 9), 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 defintion[10] 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

10.8.4. 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 8.1.2.1),

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.

10.9. Appendix 9: 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.

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (20 May 2020)

Overall Rationale for the Amendment: To address regulatory feedback on the study design and eligibility criteria.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis Objectives and Endpoints, Overall Design; 1.3 Schedule of Activities; 3 Objectives and Endpoints; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 6.3 Measures to Minimize Bias; 8.1.1 Immunogenicity Assessments; 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms; 8.5 Biomarkers; 9.4.5 Other Analyses; 10.2.7 Publication Policy	Study visit added at 28 days after onset of symptoms for participants with SARS-CoV-2 infection, with clinical examination and collection of blood samples to assess the humoral immune response and other biomarkers (RNA-seq). For comparison with biomarkers at baseline, a whole blood sample will be collected in PAXgene tubes for all participants instead of a subset. An exploratory objective and endpoint was added for evaluation of the immune response in vaccinated individuals after natural infection and to explore other potentially informative biomarkers.	Based on regulatory feedback to examine the clinical course, and immune response and other biomarkers, after SARS-CoV-2 infection.
1.2 Schema; 1.3.3 and 1.3.4 Schedule of Activities Cohorts 2a and 2b; 8 Study Assessments and Procedures	Added safety and immunogenicity visit at 7 days after each study vaccination in Cohorts 2a and 2b.	To allow additional comparisons of the immune response to vaccination in the 1-dose and 2-dose primary regimens with single booster vaccination.
1.1 Synopsis Overall Design, Statistical Methods; 4.1 Overall Design; 9.5 Planned Analysis	It was clarified that all participants in Cohort 1 could be randomized and vaccinated in the absence of safety concerns from the review of 24-hour safety data from the first 5 sentinel participants in Cohort 1a. It was also clarified that randomization and vaccination of participants in Cohort 3 could begin in the absence of safety concerns from review of 7-day safety data from the first 15 participants in Cohort 1a.	Based on regulatory feedback on the safety data required to fully enroll Cohort 1 and initiate enrollment of Cohort 3.
1.1 Synopsis Objectives and Endpoints, Overall Design; 3 Objectives and Endpoints; 4.1 Overall Design; 4.3 Justification for Dose; 6.1 Study Vaccinations Administered	The Ad26.COV2.S dose level for vaccination in Cohort 2a was revised to 1×10^{11} vp. It was also clarified that the volume administered to participants in Cohort 2 would be 1 mL.	To allow assessment in Cohort 2 of a 1-dose primary regimen and booster vaccination with each vaccination at a dose level 1×10^{11} vp, and comparison with a 2-dose primary regimen and booster vaccination with each vaccination at a dose level of 5×10^{10} vp.
5.1 Inclusion Criteria; 5.2 Exclusion Criteria; 10.1 Abbreviations; 11 References	Eligibility criteria were revised to clarify that participants will not have underlying comorbidities that increased the risk of severe COVID-19.	Based on regulatory feedback to exclude participants who would be at higher risk of severe COVID-19.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria; 6.8 Prestudy and Concomitant Therapy; 7.1 Discontinuation of Study Vaccination	Exclusion criterion 9 was clarified to specify that participants on current treatment with investigational agents for prophylaxis of COVID-19 will be excluded. Text was revised to clarify that any participant who received anti-COVID-19 vaccine or treatment will not receive further study vaccination.	Based on regulatory feedback to exclude such participants.
5.2 Exclusion Criteria	Exclusion criterion added to exclude participants currently working in occupation with high risk of exposure to SARS-CoV-2 from Cohorts 1 and 3.	Based on regulatory feedback to exclude such participants from Cohorts 1 and 3.
1.1 Synopsis Overall Design; 1.3.6 Procedures for Participants with COVID-19-like Signs and Symptoms; 4.1 Overall Design; 8 Study Assessments and Procedures; 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms; 9.4.5 Other Analyses; 10.1 Abbreviations; 10.2.10 Source Documents	The Global Impression of Severity and Global Impression of Change were removed from the procedures in case of COVID-19-like symptoms. The name of the COVID-19 Signs and Symptoms Instrument (CSSI) was updated to the Symptoms of Infection with COVID-19 (SIC).	To reflect changes made to the PRO assessments in the study.
6.9 Study Vaccination Pausing Rules	Study vaccination pausing rules were revised to remove temporal requirements.	Based on regulatory feedback that temporal requirements should be included in the assessment of causality.
1.1 Synopsis Statistical Methods; 9.2 Sample Size Determination	The probability of observing an AE based on possible true AE incidences was revised to reflect the number of active vaccine recipients in Cohorts 2a and 2b.	To reflect the number of active vaccine recipients in Cohorts 2a and 2b in the description of the safety assessment provided by the study sample size.
4.1 Overall Design	Details were added on the estimation of an over-enrollment rate for seronegative participants in the absence of a serological test at screening.	To provide more details on the over-enrollment of seronegative participants, if needed.
2.3.1 Risks Study Participation; 9.5 Planned Analysis	Clarification added that a prespecified threshold for the imbalance in molecularly confirmed COVID-19 cases to trigger DRC notification will be described in the Statistical Analysis Plan.	Based on regulatory feedback to clarify that this threshold will be described in the Statistical Analysis Plan.
4.2 Scientific Rationale for Study Design; 6.3 Measures to Minimize Bias	Details were added on the possible initial use of a paper randomization list if the IWRS is not live at the planned time of randomization of the first participant.	A paper randomization list could initially be used until IWRS is live.
8 Study Assessments and Procedures	Added eCRF guidelines to list of study-specific materials.	To provide more information on material for investigator.
General	Minor errors and inconsistencies were corrected throughout the protocol.	Correction of minor errors and inconsistencies.

Amendment 2 (5 June 2020)

Overall Rationale for the Amendment: To address regulatory agency feedback on the study design.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall Design, Number of Participants, Statistical Methods; 1.3 Schedule of Activities; 4.1 Overall Design; 9.2 Sample Size Determination; 9.5 Planned Analysis	The number of participants in Cohorts 1a and 3 was increased. In addition, the number of participants for whom peripheral blood mononuclear cells (PBMCs) will be collected was increased in Cohorts 1a and 3.	To generate additional immunogenicity data in Cohorts 1a and 3 based on regulatory agency feedback.
5.1 Inclusion Criteria	The age for participants to be enrolled in Cohort 3 was revised to 65 to 75 years inclusive for study sites in Belgium.	Based on regulatory agency feedback.
1.1 Synopsis, Overall Design; 1.3 Schedule of Activities; 4.1 Overall Design; 6.8 Prestudy and Concomitant Therapy; 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms	The recording of concomitant medications was added to the procedures for the study visit conducted 28 days after symptom onset for participants with a positive test result for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.	To obtain additional information on coronavirus disease-2019 (COVID-19) cases.
1.3 Schedule of Activities; 8 Study Assessments and Procedures	The time period from screening after which the nasal swab sample and, if available, serological test for SARS-CoV-2-specific antibodies are to be repeated on Day 1 was increased from 2 days to 3 days.	To allow more flexibility in the screening process.
8 Study Assessments and Procedures	The maximum blood volume to be collected was clarified.	To account for the possibility of blood samples being collected in case of COVID-19-like signs and symptoms.
1.1 Synopsis, Dosage and Administration; 6.1 Study Vaccinations Administered	Clarification was added that Ad26.COV2.S will be supplied as a suspension in single-use vials.	To provide more information on Ad26.COV2.S vaccine.
4.3 Justification for Dose	Text was revised to clarify the highest dose level of adenovirus type 26 (Ad26)-based vaccines previously evaluated in clinical studies.	To clarify the reasons for dose level selection.
10.1 Abbreviations; 10.2.8 Data Quality Assurance	Text describing data quality assurance was revised.	To clarify the processes to be followed for data quality assurance / quality control.
1.1 Synopsis, Statistical Methods; 9.5 Planned Analysis	Although the assay will still be conducted, references to the antibody-dependent cellular phagocytosis (ADCP) assay were removed from the description of the interim and primary analyses.	To focus the description of immunogenicity data in the interim and primary analyses on virus neutralization assay (VNA), enzyme-linked immunosorbent assay (ELISA), and T-helper (Th)1/Th2 assays.
2.2 Background	Revisions were made to the text describing clinical safety experience with Ad26-based vaccines.	To align text to standard wording used for documents in the Ad26.COV2.S clinical development program.

Amendment 3 (8 July 2020)

Overall Rationale for the Amendment: To address regulatory agency feedback on the study design and eligibility criteria.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.3 Schedule of Activities (SoA), 1.2 Schema, 4.1 Overall Design, 4.4 End of Study Definition, 8 Study Assessments and Procedures, 8.1.3 Efficacy Assessments, 9.5 Planned Analysis	Extension of follow up to at least 1 year after the last vaccine dose in all participants to further evaluate safety (including the risk of vaccine-enhanced disease), to assess the durability of immune response, and to maximize the opportunity of obtaining preliminary data on possible efficacy after SARS-CoV-2 exposure.	Based on regulatory agency feedback.
1.1 Synopsis, 1.3 Schedule of Activities (SoA), 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 and Serious Adverse Events	After each vaccination, participants should remain under observation at the study site for at least 1 hour (instead of 30 minutes) for the presence of any acute reactions and solicited events.	Based on regulatory agency feedback.
1.1 Synopsis; 4.1 Overall Design,	It has been clarified in the protocol that, if the immunogenicity results obtained after the 1st vaccination in Cohort 1a are not adequately supporting initiation of Cohort 2, then results obtained after the 2nd vaccination in the 2-dose regimens in Cohort 1a will be used to select the vaccine regimens to be evaluated in Cohort 2 of this study. If the immunogenicity results obtained after the 2nd vaccination in the 2-dose regimens in Cohort 1a do not demonstrate an adequately increased immune response, the sponsor will not provide the 2nd vaccination at Day 57 in Cohort 2 of this study.	Based on regulatory agency feedback.
1.3 Schedule of Activities (SoA), 2.3.3 Benefit-Risk Assessment of Study Participation, 5 Study Population	Eligibility will be reassessed pre-vaccination on Day 1.	Based on regulatory agency feedback.
1.3 Schedule of Activities (SoA), 2.3.3 Benefit-Risk Assessment of Study Participation, 5.1 Inclusion Criteria, 8.2.4 Clinical Laboratory Assessments, 9.4.2 Primary Endpoints, 10.2 Appendix 2: Clinical Laboratory Tests	Addition of a clinical laboratory assessment (blood and urine) at screening, pre-vaccination at each day of vaccination (pre-dose 1 and pre-dose 2), and at the Day 7 post vaccination visit for the primary regimens (Day 8 and Day 64).	Based on regulatory agency feedback.
1.3 Schedule of Activities (SoA), 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Clarified that SAEs will be reported until the end of the study for all participants.	Based on regulatory agency feedback.

Section Number and Name	Description of Change	Brief Rationale
1.3.6 Procedures for Participants With COVID-19-like Signs and Symptoms; 4.1 Overall Design; 8 STUDY ASSESSMENTS AND PROCEDURES; 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms; 8.1.2.1 Prespecified Criteria for Suspected COVID-19	Prespecified criteria for suspected COVID-19 are added and updated.	Based on regulatory agency feedback.
5.1 Inclusion Criteria	Obesity is a risk factor of severe COVID-19. The criterion 'Participant must have a body mass index (BMI) <40.0 kg/m^2' has been updated to ≤30.0 kg/m^2 as per CDC definition of obesity.	Based on regulatory agency feedback.
5.2 Exclusion Criteria 4.1 Overall Design	Several exclusion criteria were updated. Since a serological test to detect SARS-CoV-2 specific antibodies will be available, the paragraph on over-enrollment has been removed from Section 4.1.	Based on regulatory agency feedback.
10.7 Appendix 7: Symptoms of Infection with Coronavirus-19 (SIC)	Section 10.7, Appendix 7 has been added with an example SIC.	For consistency across protocols.
Throughout the protocol	• Ad26.COV2.S will be used as primary compound ID instead of Ad26COVS1. • Minor errors and inconsistencies were corrected throughout the protocol.	• Change of vaccine name in the company development program. • Correction of minor errors and inconsistencies.

Amendment 4 (6 August 2020)

Overall Rationale for the Amendment: To address EC feedback on nasal swab sampling. In addition, clarification to the eligibility criteria on blood pressure for the elderly population (Cohort 3) was included. Furthermore, minor errors and inconsistencies were corrected throughout the protocol.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.3.6 Procedures for Participants with COVID-19-like Signs and Symptoms, 4.1 Overall Design, 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms, 8.1.2.1 Prespecified Criteria for Suspected COVID-19	It has been clarified in the protocol that the nasal swab sample should be taken by a health care professional for study sites in Belgium.	Based on Belgian EC feedback.
5.1 Inclusion Criteria, 5.2 Exclusion Criteria	Clarification added to the eligibility criteria on blood pressure for the elderly population (Cohort 3).	Clarification.
1.1 Synopsis, 3 Objectives and Endpoints, 8.1.1 Immunogenicity Assessments	ELISpot has been moved from secondary to exploratory endpoints.	At the time of protocol amendment 3, the sponsor intended to use ICS or ELISpot for the determination of Th1 and Th2 responses. The sponsor has decided to keep the ICS as the primary cellular assay for assessment of Th1 and Th2 responses. In order to reinforce our Th1/Th2 response assessment, the sponsor has now decided to also include IFNγ and IL-4 ELISpot as an exploratory endpoint to support the secondary cellular endpoint assessed by ICS.
1.3 Schedule of Activities, 8 Study Assessments and Procedures	Add flexibility to allow a window up to 4 days for availability of serology test for presence of SARS-CoV-2-specific antibodies and confirmatory PCR test for the presence of SARS-CoV-2 infection before start of the first vaccination. In addition, the same window will apply to clinical laboratory testing and urinalysis.	Operational request.
6.8 Prestudy and Concomitant Therapy	It has been clarified in the protocol that participants should be instructed to take antipyretics at the first signs of symptoms post vaccination	DRC recommendation.
1.1 Synopsis, 4.1 Overall Design, 9.5 Planned Analysis	Added “approximately” to the target number of participants to be enrolled in each cohort.	Operational request.

Section Number and Name	Description of Change	Brief Rationale
10.8 Appendix 8: Case Definitions for COVID-19, 10.9 Appendix 9: Symptoms of Coronavirus (US Centers for Disease Control and Prevention)	Case definitions for COVID-19 have been aligned with the Phase 3 protocols. In addition, "new loss of taste or smell" was added to the case definition of mild disease at the recommendation of the NIH	Alignment and NIH request.
Throughout the protocol	Minor errors and inconsistencies were corrected throughout the protocol.	Correction of minor errors and inconsistencies.

Amendment 5 (13 August 2020)

Overall Rationale for the Amendment: To address HA feedback on the eligibility criteria on blood pressure for the elderly population (Cohort 3).

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria, 5.2 Exclusion Criteria	Cohort 3 participants, ie, 65 year-olds or older, with mild hypertension or high blood pressure will only be included in the study, as long as their symptoms and signs are stable and medically controlled as defined by no change in medication over the past 6 months (except for issues of tolerability or use of similar drug with same mechanism of action eg, thiazides, Beta blockers, Alpha blockers at the same effective dose).	Upon HA request.
5.2 Exclusion Criteria	Numbering of exclusion criteria 23, 25 and 26 was corrected.	Correction.

11. REFERENCES

1. Adenoviral Vaccine Safety Database V5.0. Janssen Vaccines & Prevention B.V. 10 April 2020.
2. Agrawal AS, Tao X, Algaissi A, et al. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. Hum Vaccin Immunother. 2016;12(9):2351-2356.
3. Anywaine Z, Whitworth H, Kaleebu P, et al. Safety and Immunogenicity of a 2-Dose Heterologous Vaccination Regimen With Ad26.ZEBOV and MVA-BN-Filo Ebola Vaccines: 12-Month Data From a Phase 1 Randomized Clinical Trial in Uganda and Tanzania. J Infect Dis. 2019;220(1):46-56.
4. Barouch DH, Liu J, Peter L, et al. Characterization of humoral and cellular immune responses elicited by a recombinant adenovirus serotype 26 HIV-1 Env vaccine in healthy adults (IPCAVD 001). J Infect Dis. 2013:207(2);248-256.
5. Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). Lancet. 2018;392(10143):232-243.
6. Belgian Red Cross. https://www.rodekruis.be/. Accessed 12 April 2020.
7. Bolles M, Deming D, Long K, et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85(23):12201-12215.
8. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). Groups at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-athigher-risk.html. Accessed 7 May 2020.
9. Center for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) Symptoms and Complications. https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html. Accessed 15 February 2020.
10. Center for Disease Control and Prevention. Symptoms of Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed 8 July 2020.
11. Center for Disease Control and Prevention COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12–April 2, 2020. Morb Mortal Wkly Rep 2020;69:422–426.
12. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin. Microbiol. Rev. 2015; 28(2):465–522.
13. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
14. Chen Z, Zhang L, Qin C, et al. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J Virol. 2005;79(5):2678-2688.
15. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660-694.
16. Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol. 1969;89(4);449-463.
17. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536-544.
18. Deming D, Sheahan T, Heise M, et al. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. PLoS Med. 2006;3(12):e525.
19. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020 Mar 16. pii: e20200702. [Epub ahead of print]

20. European Centre for Disease Prevention and Control. Factsheet for health professionals on coronaviruses. https://www.ecdc.europa.eu/en/factsheet-health-professionals-coronaviruses. Accessed 15 February 2020.

21. Faber M, Lamirande EW, Roberts A, et al. A single immunization with a rhabdovirus-based vector expressing severe acute respiratory syndrome coronavirus (SARS-CoV) S protein results in the production of high levels of SARS-CoV-neutralizing antibodies. J Gen Virol. 2005;86(Pt 5):1435-1440.

22. Fulginiti VA, Eller JJ, Sieber OF, Joyner JW, Minamitani M, Meiklejohn G. Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. Am J Epidemiol. 1969:89(4);435-448.

23. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 States. Morb Mortal Wkly Rep 2020;69:458–464.

24. Gidudu JK, Walco GA, Taddio A, et al./The Brighton Immunization Site Pain Working Group. Immunization site pain: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012:30(30);4558-4577.

25. Honda-okubo Y, Barnard D, Ong CH, Peng BH, Tseng CT, Petrovsky N. Severe acute respiratory syndrome-associated coronavirus vaccines formulated with delta inulin adjuvants provide enhanced protection while ameliorating lung eosinophilic immunopathology. J Virol. 2015;89(6):2995-3007.

26. Houser KV, Broadbent AJ, Gretebeck L, et al. Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody. PLoS Pathog. 2017;13(8):e1006565.

27. Investigator's Brochure: Ad26COVS1 (VAC31518), Edition 1.0. Janssen Vaccines & Prevention B.V.

28. Janssen Vaccines & Prevention B.V. Data on file.

29. Johns Hopkins CSSE. Coronavirus COVID-19 Global Cases. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed 29 April 2020.

30. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol. 1969:89;405-421.

31. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969:89(4);422-434.

32. Kohl KS, Walop W, Gidudu J, et al./The Brighton Collaboration Local Reaction Working Group for Swelling at or near Injection Site. Swelling at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine 2007:31;5858-5874.

33. Kohl KS, Walop W, Gidudu J, et al./The Brighton Collaboration Local Reaction Working Group for Induration at or near Injection Site. Induration at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine 2007:31;5839-5857.

34. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5:562–569.

35. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382(13):1199-1207.

36. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Jan 30. pii: S0140-6736(20)30251-8.

37. Marcy SM, Kohl KS, Dagan R, et al./The Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004:22(5-6);551-556.

38. Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia ankara-vectored ebola vaccines: a randomized clinical trial. JAMA. 2016:315;1610-1623.

39. Modjarrad K, Roberts CC, Mills KT, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. Lancet Infect Dis. 2019;19(9):1013-1022.

40. Moghaddam A, Olszewska W, Wang B, et al. A potential molecular mechanism for hypersensitivity caused by formalin-inactivated vaccines. Nat Med. 2006:12(8);905-907.

41. Smatti MK, Al Thani AA, Yassine HM. Viral-Induced Enhanced Disease Illness. Front Microbiol. 2018;9:2991.

42. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. September 2007. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf. Accessed 19 February 2020.

43. US Department of Health and Human Services. Office for Human Research Protections - OHRP Expedited Review Categories. 1998. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categoriesof-research-expedited-review-procedure-1998/index.html. Accessed 24 February 2020.

44. US Food and Drug Administration. Conditions for IRB Use of Expedited Review. Federal Register: November 9, 1998 (Volume 63, Number 216). https://www.fda.gov/science-research/guidance-documentsincluding-information-sheets-and-notices/conditions-irb-use-expedited-review. Accessed 24 February 2020.

45. Wang D, Hu B, Hu C. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1585. [Epub ahead of print].

46. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). Accessed 15 February 2020.

47. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 12 March 2020.

48. World Health Organization. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations, October 2004. https://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1/en/. Accessed 15 February 2020.

49. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269.

50. Zhao J, Alshukairi AN, Baharoon SA, et al. Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. Sci Immunol. 2017;2(14). pii: eaan5393.

51. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.

52. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-347.

INVESTIGATOR AGREEMENT

VAC31518 JNJ-78436735 Clinical Protocol VAC31518COV1001 Amendment 6

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): Jerry 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, email=jsadoff@its.jnj.com, c=US Reason: I am approving this document Date: 2020.09.19 07:00:16 -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. 147

Status: Approved, Date: 19 September 2020

Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26COVS1 in Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older

Protocol VAC31518COV1001; Phase [1/2a]

VAC31518 (JNJ-78436735)

Status:	Approved
Date:	20 August 2020
Prepared by:	Janssen Vaccines & Prevention B.V.
Document No.:	EDMS-RIM-102684

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

CHANGES TO PREVIOUS VERSIONS

TABLE OF CONTENTS

VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	20-Aug-2020	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the pre-planned analyses for the Data Review Committee (DRC), Interim Analyses, Primary Analyses, Final Analysis and End of Study Analysis, for all cohorts in the study. One or several Data Presentation Specification Documents (DPS) will be available to further detail the statistical outputs that will be generated.

For some analyses (e.g. RNA sequencing data, passive transfer study), a separate SAP may be written.

2. OBJECTIVES AND ENDPOINTS

Refer to Clinical Trial Protocol (CTP) Section 3.

3. TRIAL DESIGN

Refer to CTP Section 4.

4. STATISTICAL HYPOTHESES

Refer to CTP Section 9.1.

5. SAMPLE SIZE DETERMINATION

Refer to CTP Section 9.2.

6. POPULATIONS FOR ANALYSIS

For vaccine studies, study intervention assignment will follow the as treated principle: all analyses (including safety, immunogenicity and efficacy analyses) will be analyzed by the actually received vaccine.

Population	Description
All screened participants (ALL)	The "all screened participants" set includes all participants that were screened, regardless of whether they were enrolled and/or randomized.
All randomized participants (ALL RANDOMIZED)	The "all randomized participants" set includes all participants that were randomized to one of the treatment groups.
Full Analyses Set (FAS)	The full analysis set will include all participants with at least one vaccine administration documented.
Per Protocol Immunogenicity Set (PPI)	The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural infection occurring after screening (if applicable) will be excluded from the analysis set.
Per Protocol Efficacy Set (PPE)	The per protocol efficacy population will include all randomized participants having received at least 1 vaccination for whom efficacy data concerning endpoint measures are available. All efficacy analyses will be done according to the as treated principle (ie, actually received vaccinations).

7. STATISTICAL ANALYSES

7.1. General Considerations

7.1.1. Study phases

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

The safety analysis will present all results by phase (cf. section 7.1.2 for phase definitions). Immunogenicity results will be presented per scheduled time point as appropriate. Efficacy analyses will present results by phase or pooled for the entire study, 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).

7.1.2. Phase definitions

The phase definitions are different by cohort. For cohorts in which two vaccinations are administered in the primary regimen and having no booster doses (cohorts 1a, 1b and 3), the phases in the study will be constructed as detailed in Table 1.

Table 1: Phase Definitions for cohorts 1a, 1b, and 3

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
Regimen	2	Post-dose 1	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 database cut-off in case of interim analysis c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to post-dose 2
Follow-up 1	3			One minute after Post dose 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post dose 2
Regimen	2	Post-dose 2	2	Date and time of second vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the second vaccination (23:59 of day of vaccination + 28 days)
Follow-up 2	4			One minute after Post-dose 2 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 at the date of last visit

Note: the end date of the regimen phase should be the end date of the last post dose period.

For cohort 2a, the phases will be defined as detailed in Table 2.

Table 2: Phase Definitions for cohort 2a

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
Regimen	2	Post-dose 1	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 database cut-off in case of interim analysis c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to post-dose 2
Follow-up 1	3			One minute after Post dose 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post booster 1
Regimen	2	Post-booster 1	2	Date and time of first booster vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the first booster vaccination (23:59 of day of vaccination + 28 days)
Follow-up 2	4			One minute after Post-booster 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post booster 2
Regimen	2	Post-booster 2	3	Date and time of second booster vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the second booster vaccination (23:59 of day of vaccination + 28 days)
Follow-up 3	5			One minute after Post-booster 2 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off date in case of interim analysis c) One minute prior to post booster 3
Regimen	2	Post-booster 3	4	Date and time of third booster vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis

					c) 23:59 on Day 28 after the third booster vaccination (23:59 of day of vaccination + 28 days)
Follow-up 4	6			One minute after Post-booster 3 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 at the date of last visit

Note: the end date of the regimen phase should be the end date of the last post dose period.

For cohort 2b, the phases will be defined as detailed in Table 3.

Table 3: Phase Definitions for cohort 2b

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
Regimen	2	Post-dose 1	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 database cut-off in case of interim analysis c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to post-dose 2
Follow-up 1	3			One minute after Post dose 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post dose 2
Regimen	2	Post-dose 2	2	Date and time of second vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the second vaccination (23:59 of day of vaccination + 28 days)
Follow-up 2	4			One minute after Post-dose 2 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post booster 1
Regimen	2	Post-booster 1	3	Date and time of first booster vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the first booster vaccination (23:59 of day of vaccination + 28 days)

Follow-up 3	5			One minute after Post-booster 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post booster 2
Regimen	2	Post-booster 2	4	Date and time of second booster vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the second booster vaccination (23:59 of day of vaccination + 28 days)
Follow-up 4	6			One minute after Post-booster 2 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) One minute prior to post booster 3
Regimen	2	Post-booster 3	5	Date and time of third booster vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on Day 28 after the third booster vaccination (23:59 of day of vaccination + 28 days)
Follow-up 5	7			One minute after Post-booster 3 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 at the date of last visit

Note: the end date of the regimen phase should be the end date of the last post dose period.

Adverse Events and selected other tables may display AEs (or other counts) by period. For such tables, active periods can be combined and additionally displayed. Depending on the primary regimen (one or two doses; presence or absence of booster doses), the active periods can be:

- "Post-Dose 1"
- "Post-Dose 2" (does not exist in Cohort 2a)
- "Post-Dose 1 and Post-Dose 2 Combined", which refers to the "primary regimen". If the primary regimen is a one-dose regimen (Cohort 2a), then this combined period will not exist and should also not be displayed.
- "Post-Booster 1" (only in cohorts 2a and 2b)
- "Post-Booster 2" (only in cohorts 2a and 2b)
- "Post-Booster 3" (only in cohorts 2a and 2b)
- "Post-Dose 1 and Post-Booster Doses Combined", which refers to the complete regimen including all the booster doses in Cohort 2a. It includes the 28-day period after each vaccination (dose 1, booster dose 1, booster dose 2, and booster dose 3).

– "Post-Dose 1, Post-Dose 2 and Post-Booster Doses Combined", which refers to the complete regimen including all the booster doses in Cohort 2b. It includes the 28-day period after each vaccination (dose 1, dose 2, booster dose 1, booster dose 2, and booster dose 3).

For some tables, e.g. SAE tables, a period "Entire study" will be defined. This will be a combination of all the active phases and periods, so that it covers the time window from vaccination 1 up to and including the end of the study (per participant).

The primary endpoint includes SAEs from the first vaccination until 6 months after completion of the primary regimen for cohorts 2a and 2b. This will be a combined period of post-dose 1 and post-dose 1 Follow Up (FU) (for Cohort 2a) and a combination of post-dose 1, post-dose 1 FU, post-dose 2, and post-dose 2 FU (for Cohort 2b). This period will be labeled "Entire Primary Regimen" or similar in the outputs.

The exploratory endpoints include SAEs from the first booster vaccination time point until the end of the regimen for Cohort 2. This will be a combined period of post-booster 1 until the last follow-up period in Cohorts 2a and 2b. This period will be labeled "Entire Booster Regimen" or similar in the outputs.

7.1.3. Pooling Algorithm for Analysis Centers

Data will be pooled across the different centers.

7.1.4. Visit windows

Refer to CTP section 8. Visit windows will be taken into account for the analysis of immunogenicity results, see section 7.7.1.

7.1.5. Analyses by cohort and pooled across cohorts

All analyses are planned to be performed within each cohort separately, unless explicitly indicated that data will be pooled across cohorts.

7.2. 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 vaccine regimen and overall:

- participants screened
- participants in the FAS
- participants vaccinated and not randomized
- participants randomized and not vaccinated
- participants in the PPI
- participants in the PPE
- participants who discontinued study

- participants who discontinued vaccination
- reasons for termination

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

7.2.1. Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.
Table 4 presents a list of the demographic and baseline variables that will be summarized by vaccine regimen and overall for the FAS.

Table 4: 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	
Sex (male, female, undifferentiated)	Frequency distribution with the number and percentage of participants in each category.
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)	
Study center	
SARS-CoV-2 Seropositivity status at screening	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

7.2.2. Protocol Deviations

Major protocol deviations will be summarized. Major protocol deviations which have a potential impact on immunogenicity will be flagged in the listings.

7.2.3. Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

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 of a completely missing start date, the concomitant therapy will be considered as having started before the trial.
- 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.

Participants with COVID-19-like signs and symptoms will collect concomitant medications since symptom onset. These will be tabulated and listed; they will also be included in the programmed patient narratives.

7.3. Primary Endpoint(s) Analysis

The primary endpoints in this study, are:

All participants in Cohorts 1, 2, and 3:

- Solicited local and systemic adverse events (AEs) for 7 days after each vaccination in the primary regimen
- Unsolicited AEs for 28 days after each vaccination in the primary regimen
- For the primary endpoint: Serious adverse events (SAEs) from the first vaccination until 1 year after the second vaccination for Cohorts 1 and 3, and until 6 months after the primary regimen for Cohort 2

7.3.1. Definition of Endpoint(s)

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.

7.3.2. Estimand

Not applicable

7.3.3. Analysis Methods

Refer to section 7.6.

7.4. Secondary Endpoint(s) Analysis

7.4.1. Key/Confirmatory Secondary Endpoint(s)

The secondary endpoints in this study, are:

Humoral Immune Response

All participants in Cohorts 1, 2, and 3:

- SARS-CoV-2 neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay (VNA [wild-type virus and/or pseudovirion expressing S protein])
- SARS-CoV-2-binding antibodies measured by enzyme-linked immunosorbent assay (ELISA): Analysis of antibodies binding to the SARS-CoV-2 S protein.

Cellular Immune Response

A subset of participants in Cohorts 1, 2, and 3:

- Th1 and Th2 immune responses as assessed by flow cytometry after SARS-CoV-2 S protein peptide stimulation of peripheral blood mononuclear cells (PBMCs) and intracellular staining [ICS] including CD4+/CD8+, IFNγ, interleukin [IL] 2, TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.

7.4.1.1. Definition of Endpoint(s)

Refer to section 7.7.1.

7.4.1.2. Estimand(s)

Not Applicable

7.4.1.3. Analysis Methods

Refer to section 7.7.1.

7.5. Tertiary/Exploratory Endpoint(s) Analysis

The exploratory endpoints in this study, are:

Safety and Reactogenicity:

All participants in Cohort 2:

- Solicited local and systemic AEs for 7 days after each booster vaccination time point
- Unsolicited AEs for 28 days after each booster vaccination time point
- SAEs from the first booster vaccination time point until the end of the study

Humoral Immune Response:

Exploratory analyses may include the following assays for a subset of participants in Cohorts 1 and 3:

- SARS-CoV-2 neutralization as assessed by alternative SARS-CoV-2 neutralization assays (different from the VNA used for the secondary endpoint).
- Adenovirus neutralization.
- Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping).
- Epitope-specificity characterization for B- and T-cells.

- Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma.
- Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model.

Cellular Immune Response:

Exploratory analyses may include the following assays for a subset of participants in Cohorts 1, 2, and 3:

- Single IFNγ and IL-4 enzyme-linked immunospot (ELISpot) assay after stimulation of PBMCs with SARS-CoV-2 S protein peptides.
- Analysis of gene expression in cells stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells (ex vivo).
- Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells (ex vivo).

A subset of participants in Cohort 2 only:

- Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube-isolated PBMCs).

In addition to these immunogenicity-related exploratory endpoints, the following efficacy-related exploratory endpoints are defined in this study:

- The number of molecularly confirmed COVID-19 cases in Ad26.COV2.S versus placebo recipients in the overall study
- The number of participants with positive non-S protein ELISA (eg, N ELISA), if such an assay can be developed, in the Ad26.COV2.S and placebo groups
- Presence and severity signs and symptoms of COVID-19
- Confirmation of SARS-CoV-2 infection by molecular testing

The following endpoints are defined to examine the immune response in vaccinated individuals after natural infection and to explore other potentially informative biomarkers (eg, those associated with more severe disease):

- Confirmation of SARS-CoV-2 infection by molecular testing
- SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein)
- SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein
- Functional and molecular antibody characterization
- Analysis of gene expression by RNA transcript profiling

7.6. (Other) Safety Analyses

Safety analyses will be performed on the FAS. Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), standard deviation (SD), standard error (SE), 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.

Safety data will be analyzed by study intervention regimens as designed per protocol[a]. In addition, safety data will be analyzed by intervention regimens as designed per protocol and participant seropositivity status at screening. Data will be presented by period (post Dose 1, post Dose 2, post Booster 1, post Booster 2, and post Booster 3, as applicable) as well as over the entire regimen, and for Cohorts 2a and 2b over the entire primary regimen and over the entire booster regimen. Denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

Exploratory analyses by age (e.g. 18-40 years and 41-55 years) may be performed in Cohort 2.

7.6.1. Adverse Events

7.6.2. Definitions

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 each vaccination will be presented in the safety tables except for SAEs, which will be captured and tabulated in the outputs covering the whole study period. All other collected unsolicited adverse events will be presented through listings.

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

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 3.

[a] As indicated previously, all analyses, including the safety analyses, will be conducted by actually received vaccine ("as treated" principle). The sentence "by study intervention regimens as designed per protocol" indicates that the statistical tables are designed with the planned vaccine regimens as columns. Therefore, participants who receive e.g. "Placebo, Placebo" instead of "Ad26.COV2.S $5x10^{10}$ vp, Placebo" will appear in the "Placebo, Placebo" column. However, to avoid sparse columns, participants who receive e.g. "Placebo, Ad26.COV2.S $5x10^{10}$ vp" (which is not a planned vaccine regimen) will be excluded from the statistical tables. They will be included in the listings, as well as in the programmed patient narratives where they will appear as "Subjects with vaccine misallocation".

7.6.3. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated. 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 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, the following tables will be provided: summary table (including SAE, fatal outcome, and discontinuation), all events, most frequent, at least grade 3, permanent stop of vaccine, related, and SAE.

As a general remark, COVID-19 cases will be analyzed separately (see section 7.7.3).

- SAEs that are COVID-19 related will not be included in the SAE tables, but will be included and flagged in the SAE listings. In MedDRA version 23.0, Preferred Terms (PT codes) "COVID-19 (10084268)", "COVID-19 pneumonia (10084380)", "Suspected COVID-19" (10084451), "Asymptomatic COVID-19 (10084459)", "Coronavirus infection" (10051905), "Severe acute respiratory syndrome" (10061982), "SARS-CoV-2 carrier" (10084461), "Exposure to SARS-CoV-2" (10084456), and "Occupational exposure to SARS-CoV-2" (10084394) will be considered COVID-19 related AEs[a].
- Adverse events that are not SAEs and are COVID-19 related will not be recorded in the SDTM AE domain, but rather in the SDTM CE domain.

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

7.6.4. 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 database 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,

[a] In case this list of terms needs to be revised, the DPS will detail the revised list.

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:

1) 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.

2) 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 database 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.

3) 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 database 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.

4) 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.

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

3. Time is not considered when determining overlap of events.

7.6.5. Missing Data

Missing AE data will not be imputed. Participants who do not report an event will be considered as participants without an event. 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.

7.6.6. Laboratory, Vital Signs and Physical Examination

A listing of all laboratory values will be made, restricted to participants with at least one laboratory abnormality.

Physical examination findings will be summarized at baseline. A listing of the abnormalities will be made.

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics. Abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the FDA table in appendix 3.

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).

A listing of participants with fever according to the FDA grading table will also be provided. In addition, temperature measurements (whether obtained from the diary or from on-site assessments)

will be allocated to predefined temperature intervals (from 37.5° C until 40°C, in steps of half degree increments; eg <37.5, 37.5-<38, 38-<38.5, … >40), and tabulated.

7.7. Other Analyses

7.7.1. Immunogenicity Analyses

The analysis of immunogenicity will use the PPI set. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols). Data will be analyzed by vaccine regimen, and by vaccine regimen and participant seropositivity status at screening[a]. Data will be presented by scheduled time point. For the PPI analysis, samples taken outside of the allowed window will be excluded from the tables and graphs (but will be included in the listings and clearly marked as results not included in the PPI analyses). For the FAS analysis, samples taken outside of the allowed window will be included.

Note: analyses that are potentially unblinding at the individual participant level (e.g. graphs showing individual data tied to COVID-19 infection status, especially when the number of COVID-19 infections is low and/or when time of infection is indicated) will be carried out after official unblinding of the trial, or will be carried out exclusively on specific cohorts (or other clearly defined subgroups) after these are unblinded. Alternatively, prior to unblinding, these analyses can be performed in a completely blinded manner (e.g. tables with only a single column pooling all regimens).

7.7.1.1. Parameters

The following humoral and cellular immune responses may be measured. However, not all assays might be available for all immunogenicity analyses covered by this SAP. Further information on which assays will be analyzed in each of the analyses, will be included in the corresponding DPS documents.

[a] As indicated previously, all analyses, including the immunogenicity analyses, will be conducted by actually received vaccine ("as treated" principle). Note that the statistical tables are designed with the planned vaccine regimens as columns. Therefore, participants who receive e.g. "Placebo, Placebo" instead of "Ad26.COV2.S $5x10^{10}$ vp, Placebo" will appear in the "Placebo, Placebo" column. However, to avoid sparse columns, participants who receive e.g. "Placebo, Ad26.COV2.S $5x10^{10}$ vp" (which is not a planned vaccine regimen) will be excluded from the statistical tables. They will be included in the listings, as well as in the programmed patient narratives where they will appear as "Subjects with vaccine misallocation".

Table 5. Summary of Humoral Immunogenicity Assays

Assay	Purpose
Secondary endpoints	
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 (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S protein
Exploratory endpoints	
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other strain), as measured by an alternative neutralization assay (different from the VNA used for the secondary endpoint)
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein, if such an assay can be developed
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model

ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay

Table 6. Summary of Cellular Immunogenicity Assays

Assay	Purpose
Secondary endpoints	
Flow cytometry (ICS)	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by ICS including $CD4^+$/$CD8^+$, IFNγ, IL-2, TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers
Exploratory endpoints	
ELISpot	IFNγ and IL-4 responses to SARS-CoV-2 S protein peptides by PBMCs, based on single ELISpot
Gene expression analysis	Analysis of gene expression by RNA transcript profiling and/or analysis of protein translates, in cells or whole blood stimulated with SARS-CoV-2 S protein peptides or in unstimulated cells or whole blood (ex vivo)
Cytokine profiling (ELISA or multiplexed arrays)	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in cells or whole blood stimulated with SARS-CoV-2 S protein peptides, or in unstimulated cells or whole blood, by ELISA or multiplexed arrays and confirmation by functional in vitro assays
T and B cell phenotyping	Analysis of the phenotype of antigen-specific T and B cells, assessed by single cell analysis (on frozen or Smart tube isolated PBMCs)

ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot (assay); ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha

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

Missing immune response data will not be imputed.

Values below the lower limit of quantification (LLOQ) or limit of detection (LOD) will be handled as follows:

- Calculation of geomean and median:
  - o values<LLOQ are imputed with LLOQ/2.
- Calculation of fold increases from baseline:
  - o values <LLOQ are imputed with LLOQ.

Values above the upper limit of quantification (ULOQ) will be handled as follows:

- Calculation of geomean and median:
  - o Values>ULOQ are imputed with ULOQ.
- Calculation of fold increases from baseline:
  - o Values >ULOQ are imputed with ULOQ.

7.7.1.3. Handling of changes in assay status throughout the study conduct

In case of changes in assay status, from “qualified” to “validated”, the LLOQ and ULOQ are likely to change as well. If this should happen, then the SDTM database will contain records pertaining to the assay in the qualified status and records pertaining to the validated status, and the LLOQ and ULOQ values will also differ.

The statistical analysis will use the LLOQ and ULOQ values associated with the validated assay and will retrospectively apply these on all the data pertaining to the assay, including the data obtained while the assay status was “qualified”. This may imply that data received, statistically analyzed, and presented at an earlier time may change. Graphical displays will show the eventually used LLOQ and ULOQ values. Graphs and tables will have an additional footnote that reflects the assay status.

7.7.1.4. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

7.7.1.5. Immunogenicity against the insert

7.7.1.5.1. Humoral assays

For **VNA** (both wild-type virus and pseudovirion expressing S protein, as available), the following statistics will be calculated: N, geometric mean and corresponding 95% CI of the actual values, fold increase from baseline, fold increase from pre-dose 2 (if applicable, i.e. only for cohorts where a second dose is given in the primary regimen and for time points after dose 2), fold increase from pre-booster dose 1, fold increase from pre-booster dose 2, fold increase from pre-booster dose 3 (if applicable, i.e. only for cohorts 2a and 2b where booster doses are given and for time points after the said booster dose).

For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the $\log_{10}$ transformed values. These values are back transformed to provide the geometric mean and its corresponding 95% CI.

For wild type and pseudovirion VNA 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 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.

Reverse distribution curves of the actual values are provided for selected time points.

In the graphs, original values will be displayed on the $\log_{10}$ scale.

Further details and/or updated rules may be provided in the DPS.

For **S-ELISA**, the same as above applies.

The ratio of binding antibodies (S-ELISA) to wild type VNA, and the ratio of binding antibodies (S-ELISA) to pseudovirion expressing S protein VNA will be calculated for each time point. Values <LLOQ will be imputed with LLOQ for the calculation of the ratios. In addition, the ratio

of the fold increase from baseline in binding antibodies (S-ELISA) to the fold increase from baseline in wild type VNA, and the ratio of the fold increase from baseline in binding antibodies (S-ELISA) to the fold increase from baseline in pseudovirion expressing S protein VNA will be calculated for each post-baseline time point. Values <LLOQ will be imputed with LLOQ for the calculation of the fold increase ratios. The following statistics will be calculated and tabulated: N, geometric mean and corresponding 95% CI of the ratio. Graphical displays will also be prepared, showing – for each time point – the geometric mean of the ratio and its 95% CI, together with the individual data points (dot plot).

If a similar assay is performed at different analyzing labs, then separate statistical analyses may be performed.

Scatterplots between humoral assay results will be provided for selected time points. These may include, but are not be limited to:

- Binding antibodies (S-ELISA) versus wild type VNA
- Binding antibodies (S-ELISA) versus pseudovirion expressing S protein VNA
- Wild type VNA versus pseudovirion expressing S protein VNA

If a similar assay is performed at different analyzing labs, then the statistical analyses may distinguish between these and provide separate scatterplots for each analyzing lab versus the other assay of interest. These scatterplots will display the values as analyzed for the geometric mean calculations, with values <LLOQ imputed with LLOQ (if an LLOQ is defined) and values >ULOQ imputed with ULOQ (if an ULOQ is defined). The LLOQ and ULOQ cut-off values per assay will be visualized in the scatterplots. Spearman correlation coefficients will also be provided (one per scatterplot).

7.7.1.5.2. Cellular assays

For **ELISpot**, if available, at least the following statistics will be calculated: N, median, first and third quartile, minimum and maximum of the actual values. Additional statistics may be calculated and will be detailed in the DPS. The ELISpot in this study is planned to be two single ELISpot, measuring IFN-g and IL-4. In that case, the statistics will be analyzed for each cytokine separately.

For each cytokine, if available, the following is defined:

- Sample positivity:
  - For IFN-g: a sample will be considered positive if the value is strictly greater than the LOD (>LOD).
  - For IL-4: a sample will be considered positive if the value is strictly greater than the LOD (>LOD).
- Responder:

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

  For IFN-g:

- The baseline sample value is less than or equal to the LOD (≤LOD) and the post-baseline sample is strictly greater than the LOD (>LOD)
- The baseline sample value is strictly greater than the LOD (>LOD) and the post-baseline sample value represents an at least 3-fold (≥3-fold) increase from the baseline sample value.

For IL-4:

- The baseline sample value is less than or equal to the LOD (≤LOD) and the post-baseline sample is strictly greater than the LOD (>LOD)
- 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 2-fold (≥2-fold) increase from the baseline sample value.

The SDTM database will contain the LOD and LLOQ values.

In keeping with the general derivation rules, values <LLOQ are imputed with LLOQ/2 for the calculation of the median and with LLOQ for the calculation of the fold increases from baseline.

ELISpot values available in the database will already be background subtracted. No further background subtraction should be carried out. In case the SDTM data only contain peptide pools 1 and 2, but no combined peptide pool, then the combined peptide pool will be calculated as the sum of both peptide pools.

Tables with the descriptive statistics will be provided.

Participant profiles of the actual values over time will be graphically presented. For the graphs, original values will be displayed on the $\log_{10}$ scale.

For ELISpot, the reported values are spot forming cells per million peripheral blood mononuclear cells (PBMC).

For ELISpot, IFN-g responses are considered Th1 and IL-4 responses are considered Th2. Due to this 1-to-1 correspondence, no separate Th1/Th2 analyses will be conducted for ELISpot.

Further details and/or updated rules may be provided in the DPS.

For **ICS**, if available, at least the following statistics will be calculated: N, median, first and third quartile, minimum and maximum of the actual values, number and percentage of participants with a positive sample (if available). Additional statistics may be calculated and will be detailed in the DPS.

It is planned to analyze the following cell populations at the time of the first interim analysis. The DPS may provide an updated version of this list, e.g. for subsequent analyses.

- CD4+:
  - IFN-g or IL2

  - IFN-g or IL2 NOT TH2
  - IL4 and CD40L
  - IL4 or IL5 or IL13 and CD40L
- CD8+:
  - IFN-g or IL2

The data received from the analyzing lab(s) will contain background subtracted values ("immediately reportable values"; i.e. background subtracted[a] percentages of cells expressing the cytokine or cytokine combination). Negative background subtracted values will be imputed with zero prior to further processing.

The data will contain a positivity call for each cell population. Sample positivity should therefore not be further derived at the statistical analysis stage.

Tables will be provided that show the descriptive statistics mentioned above, structured as follows: CD4+/CD8+, peptide pool (as available in the database, e.g.: SARS-Cov2-S, SARS-Cov2-S1, SARS-Cov2-S2), cytokine (combination), and time point.

Participant profiles of the actual values over time will be graphically presented. For the graphs, original values will be displayed on the $\log_{10}$ scale, with values <0.022% imputed with 0.011% (only for visual representation; calculations will be based on the actual values). The graphs that show individual participant's data will visually differentiate between positive/negative samples (e.g. different symbols and/or different colors).

The reported values are percentage of cells expressing the cytokine(s).

Assessment of Th1/Th2 response ratio.

Based on the combined SARS-Cov2-S peptide pool, and using post baseline time points only, a Th1/Th2 response ratio will be calculated for samples that satisfy at least one of the following two conditions:

- a Th1 response ("IFN-g or IL2 NOT TH2") that is both positive and ≥ 2 x LLOQ,
- or
- a Th2 response ("IL4 or IL5 or IL13 and CD40L") that is both positive and ≥ 2 x LLOQ

For the purposes of the Th1/Th2 ratio analysis, the LLOQ is 0.022% for both cell populations (Th1 and Th2).

[a] Also known as "mock subtracted"

If both cell populations (Th1 and Th2) are positive and ≥ 2 x LLOQ, then the ratio of Th1/Th2 will be calculated as a numerical result.

If only one cell population (either Th1 or Th2) is positive and ≥ 2 x LLOQ, then the following rules will be used to determine a qualitative assessment of the Th1/Th2 ratio:

- If one cell population is positive and the other is negative, then the positive cell population is greater than the negative cell population: if the Th1 response is positive and the Th2 response is negative, then the Th1/Th2 ratio will be set to ">1". If the Th1 response is negative and the Th2 response is positive, then the Th1/Th2 ratio will be set to "<1"
- If both cell populations are positive, then the cell population that is ≥ 2 x LLOQ is greater than the cell population that is < 2 x LLOQ: if the Th1 response is ≥ 2 x LLOQ and the Th2 response is < 2 x LLOQ, then the Th1/Th2 ratio will be set to ">1". If the Th1 response is < 2 x LLOQ and the Th2 response is ≥ 2 x LLOQ, then the Th1/Th2 ratio will be set to "<1".

For each post baseline time point, the number of participants with an evaluable Th1/Th2 response ratio will be tabulated, together with the number and percentage of participants with a Th1/Th2 ratio ≥ 1 and the number and percentage of participants with a Th1/Th2 ratio < 1. Graphical display(s) of these data may also be produced.

Further details and/or updated rules may be provided in the DPS.

7.7.1.6. 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.

If only one time point is available, then actual values at that single time point will be shown as a dot plot. If multiple time points are available, then GMT plots over time, combining the regimens in one graph (without individual participant dots) will also be generated. In addition, subject profiles will then also be created.

7.7.1.7. Statistical modeling of the immune responses

Statistical modeling will be undertaken to assess the influence of demographic variables and baseline characteristics on selected immune responses. These analyses will be performed at the time of the final analysis and on the PPI analysis set, excluding participants in the regimens that received no active vaccine. The following are pre-planned statistical analyses:

- Linear regression analysis of 28 days post Dose 1, pre-Dose 2 and of 28 days post Dose 2 psVNA titers on demographic and baseline characteristics and control variables, using pooled data from all regimens and all cohorts.
  - One model for 28 days post Dose 1, one for pre-Dose 2 and one for 28 days post Dose 2
  - psVNA titers enter the model on the $\log_{10}$ scale.
  - Demographic variables: age (continuous), BMI (continuous), sex (categorical: male vs. female), race (categorical: Black or African American vs. White vs. Other).

  - Baseline characteristics: baseline SARS-CoV-2 seropositivity status (categorical: Positive vs. Negative) and baseline VNA titers against the Ad26 vector (continuous, on the $\log_{10}$ scale).
  - Control variables: single-dose vs. two-dose regimen and high-dose vs. low dose regimen.
- Linear regression analysis of 28 days post Dose 1, pre-Dose 2 and of 28 days post Dose 2 wild type VNA titers on demographic and baseline characteristics and control variables, using pooled data from all regimens and all cohorts. Same considerations as for psVNA titers.
- Linear regression analysis of 28 days post Dose 1, pre-Dose 2 and of 28 days post Dose 2 ELISA antibody concentrations on demographic and baseline characteristics and control variables, using pooled data from all regimens and all cohorts. Same considerations as for psVNA titers.
- Penalized logistic regression analysis (using Firth's method) of 28 days post Dose 1, pre-Dose 2 and of 28 days post Dose 2 responder status for psVNA on demographic and baseline characteristics and control variables, using pooled data from all regimens and all cohorts.
  - One model for 28 days post Dose 1, one for pre-Dose 2 and one for 28 days post Dose 2
  - psVNA responder status enters the model as a categorical variable (coded 1 for responder and 0 for non-responder).
  - Other considerations as for the linear regression models

7.7.2. COVID-19 case monitoring to detect imbalances across study groups (harm monitoring)

An unblinded statistician, who is not otherwise involved in the study, 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 unblinded statistician will inform the DRC as soon as an imbalance between groups is detected.

As soon as 3 confirmed COVID-19 cases have occurred, and with every additional case, the unblinded statistician will tabulate the cases according to whether the participant received Ad26.COV2.S or placebo (i.e. active regimens will be pooled) and calculate the difference in proportions between the two groups (proportion in active – proportion in placebo). Two (two-sided) confidence intervals around this difference will be constructed, a 95% CI and an 80% CI (i.e. using z-values corresponding to alpha = 0.05 and alpha = 0.20), using Newcombe's method without continuity correction.

The Newcombe's confidence interval for a difference between proportions is calculated as follows:

$$Lower\ limit: (\hat{p}_1 - \hat{p}_2) - \sqrt{(\hat{p}_1 - L_1)^2 + (U_2 - \hat{p}_2)^2}$$
$$Upper\ limit: (\hat{p}_1 - \hat{p}_2) + \sqrt{(U_1 - \hat{p}_1)^2 + (\hat{p}_2 - L_2)^2}$$

Where L_i and U_i are the Wilson Lower and Upper confidence limits for p_i. The Wilson confidence limits without continuity correction for each binomial proportion $p_i=x_i/n_i$ (i=1,2) is given by:

$$\frac{1}{2(n_i + z^2)}\left((2n_i\hat{p}_i + z^2) \pm z\sqrt{4n_i\hat{p}_i(1 - \hat{p}_i) + z^2}\right)$$

If the upper limit of the two-sided 95% CI around the difference in proportions exceeds 0.10 (i.e. >10 percentage points difference between active and placebo), and the lower limit of the two-sided 80% CI around the difference in proportions exceeds 0 (i.e. >0 percentage points difference between active and placebo), then the unblinded statistician will conclude that there is an imbalance between active and placebo (where the proportion in active is greater than the proportion in placebo). Otherwise, the statistician will not conclude that there is an imbalance.

The same operations will be executed for severe COVID-19 cases, using these definitions of "severe" cases:

- COVID-19 cases requiring hospitalization,
- COVID-19 cases requiring hospitalization and the patient being admitted to the Intensive Care Unit,
- COVID-19 cases resulting in death (with death being at least probably related to COVID-19)

7.7.3. COVID-19-like Signs and Symptoms

If a participant experiences COVID-19-like symptoms (eg, cough, feverishness, dyspnea, gastrointestinal symptoms, anosmia), the following should take place:

- Participants should contact the study site at the time of symptom onset
- A nasal swab should be collected from the participant at home (using available material for home swabs) as soon as possible and preferably no longer than 2 to 3 days after the onset of symptoms, and stored appropriately. It is preferred that the swab is taken by a caregiver (spouse, partner, relative, friend, or health care professional). If that is not possible, the participant can collect the swab him- or herself. The sample should be transferred to the study site by an appropriate method as soon as possible after being collected. A second nasal swab will be obtained 2 to 4 days after the first swab following the same procedures as the first nasal swab or at the study site if appropriate procedures are in place. The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by molecular testing using the nasal swab sample.
- Participants should complete the Symptoms of Infection with COVID-19 (SIC) and record their highest body temperature daily starting on the first day they experience symptoms. If either nasal swab is positive for SARS-CoV-2 or influenza, collection of data will continue until sign and symptom resolution. If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab.
- For participants with a positive test result for SARS-CoV 2 infection, a study visit will be conducted 28 days after symptom onset to assess the clinical course of the infection, record concomitant medications since symptom onset, and obtain a blood sample for evaluation of the immune response and other biomarkers.

The SIC asks participants to indicate, for each of 25 symptoms and on a daily basis, whether or not they experienced the symptom (Yes/No), and if Yes, to rate the severity (on an 11-point scale ranging from 0 to 10, where 0 = none to 10 = worst). In addition, 4 questions are asked that are asked to be responded to by Yes/No, without severity assessment.

The presence of SARS-CoV-2 infection and influenza infection will be assessed at the study site by molecular testing using the nasal swab sample.

<u>The following analyses will be conducted at the time of the final analysis:</u>

The number and percentage of participants with at least one molecularly confirmed SARS-CoV-2 infection will be tabulated by vaccine regimen, for the entire study period only.

The analysis will be repeated pooling all active regimens vs. placebo, where data from all cohorts will be pooled. If at least 5 molecularly confirmed SARS-CoV-2 infection are observed, vaccine efficacy (VE) will be calculated with a 90% confidence interval (CI). Otherwise, no VE will be calculated and only the above mentioned descriptive statistical analysis will be conducted. The following paragraphs provide the rationale for only calculating VE when at least 5 events are observed, as well as the formula to calculate VE and its 90% CI.

Assuming a true VE of 70%, 23 events of molecularly confirmed SARS-CoV-2 infections are required to offer 80% power to detect vaccine efficacy exceeding zero (H0: VE = 0) when using a one-sided alpha level of 0.05 (i.e. a 90% CI) and a randomization ratio of 4.65:1 (860 active:185 placebo). Assuming a true VE of 90%, 5 events are required to offer 80% power to detect vaccine efficacy exceeding zero (H0: VE = 0) when using a one-sided alpha level of 0.05 (i.e. a 90% CI) and a randomization ratio of 4.65:1 (860 active:185 placebo).

The formula to calculate VE (as a percentage) is:

$$VE = 100 \times \left(1 - \frac{p}{r(1-p)}\right)$$

Where p = proportion of events occurring among the group of participants vaccinated with Ad26.COV2.S , r = the ratio of the number participants vaccinated with Ad26.COV2.S to the number of participants vaccinated with placebo. An exact Clopper-Pearson 90% CI will be calculated.

The number and percentage of participants with at least one molecularly confirmed Influenza infection will be tabulated by vaccine regimen, for the entire study period only.

The number and percentage of participants with at least one positive non-S protein ELISA (e.g., N ELISA), if available, will be tabulated by vaccine regimen. The analysis will be repeated pooling all active regimens vs. placebo, where data from all cohorts will be pooled. If at least 5 positive non-S protein ELISA events have been observed, VE can be calculated against this endpoint, using the same approach as outlined above for the VE against molecularly confirmed SARS-CoV-2 infection.

For each participant with confirmed COVID-19 infection, a narrative will be prepared based on the visit performed 28 days after the onset of COVID-19 signs and symptoms and other selected information from the clinical database, as available:

- participant ID
- vaccination regimen
- sex, race, ethnicity, age, BMI, dates at which vaccinations were received
- physical examination findings based on the visit performed 28 days after the onset of COVID-19 signs and symptoms

- vital signs including body temperature based on the visit performed 28 days after the onset of COVID-19 signs and symptoms
- concomitant medications since symptom onset
- Humoral immune responses as collected at the planned time points + those obtained from the blood sample taken on the visit performed 28 days after the onset of COVID-19 signs and symptoms. This information may be presented graphically.

For the analysis of the SIC (Patient Reported Outcomes, PRO) data, the following considerations apply

- An "episode" is defined as a period in which any symptoms are reported on the SIC, starting from the first day on which symptoms were reported until the first day that the PRO was not completed because the symptoms had resolved (this will be indicated in the SDTM data, with reason for not completing the PRO = "Symptoms resolved" (or similar)) or death
- A symptom (e.g. feeling generally unwell, fatigue, physical weakness, cough, etc.) is assumed to be present on each day the associated Yes/No question is answered "Yes" or the associated severity question has a rating > 0.
- If the PRO was not completed due to the participant being too ill or due to the participant being hospitalized, the symptom will be considered present with severity score 10. If the PRO was not completed due to any other reason, no imputations will be done.

Duration of the episode will be calculated as episode end date – episode start date. Duration of each symptom will be calculated as last day of symptom reporting – first day of symptom reporting + 1. Duration of the maximum severity is defined as the last day of reporting the maximum severity – the first day of reporting the maximum severity + 1.

The following analyses will be conducted for confirmed SARS-CoV-2 infection cases and confirmed influenza infection cases separately:

- At the level of first episodes, the following statistics will be calculated: number of episodes, mean and median duration of episodes (with min, max, q1 and q3), and mean and median number of symptoms reported per episode (with min, max, q1 and q3).
- At the level of the symptoms for each first episode, the following statistics will be calculated: number of participants experiencing the symptom, mean and median duration of each symptom (with min, max, q1 and q3), median (with q1 and q3) of maximum severity of each symptom, median duration of the maximum severity of each symptom (with min, max, q1 and q3).
- At the level of the participants, for each episode and each symptom separately, the duration, and minimum and maximum severity scores will be tabulated (as available).

In addition, participant listings will be provided containing the SIC information for each time point.

More details about these analyses will be provided in the DPS.

7.7.4. Definition of Subgroups

Selected safety and immunogenicity analyses will be conducted by the seropositivity status (positive vs. negative) of the participant. A participant will be considered seropositive if:

1. The serological test for SARS-CoV-2-specific antibodies at baseline (if available) is positive

   Note: in case multiple test results are available (IgG, IgM, IgA, no isotype specified), then as soon as one of the test results is positive, the participant will be considered seropositive.

   OR

2. The S ELISA immunogenicity readout on Day 1 is considered positive.

At the time of first interim analysis of a cohort, S ELISA Day 1 data for that cohort may not be available at the time of the CRF database snapshot or lock. In that case, participant serostatus will be based solely on the serological test for SARS-CoV-2-specific antibodies at baseline. As of the second interim analysis, it is expected that S ELISA Day 1 data will have become available for the participants, so that both criteria can (and will) be applied.

7.8. Interim Analyses

This SAP applies to all planned analyses of this study per CTP section 9.5 (Interim Analyses; Primary Analyses; Final Analysis; and End of Study Analysis). After the first database lock, separate SAP document(s) may be written as needed to cover specific analysis needs that cannot be documented elsewhere (e.g. in the Data Presentation Specifications [DPS] document).

7.8.1. Data Review Committee (DRC) or Other Review Board

A Data Review Committee (DRC) has been commissioned to review the safety data of this trial. Please refer to the DRC Charter.

8. CHANGES FROM PROTOCOL

The protocol refers to the active vaccine as “Ad26COVS1”. This SAP uses the new reference “Ad26.COV2.S” throughout the document (including text copied from the protocol), with the exception of the protocol title which has been kept unchanged.

9. SUPPORTING DOCUMENTATION

9.1. Appendix 1 List of abbreviations

Ad26	Adenovirus serotype 26
AE	adverse event
AESI	Adverse event of special interest
BMI	Body Mass Index
CI	confidence interval
CoV	Corona Virus
COVID-19	Corona Virus Disease 2019
CRF	case report form
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DRC	Data Review Committe
eCRF	electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot (assay)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FU	Follow-up
GMC	Geometric mean concentration
GMT	Geometric mean titer
H0	Null hypothesis
ICH	International Conference on Harmonization
ICS	Intracellular cytokine staining
IFN-γ / IFN-g	Interferon gamma
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGM	Immunoglobulin M
IL	Interleukin
ITT	Intent-to-Treat
IU/ml	International units per milliliter
IVRS	interactive voice response system
IWRS	interactive web response system
kg	kilogram
LLOQ	lower limit of quantification
LOD	Limit of detection
m	meter
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number
NA	Not Applicable
PBMC	peripheral blood mononuclear cell
PD	Pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PP	Per Protocol
PPE	Per Protocol Efficacy Set
PPI	Per Protocol Immunogenicity Set
PRO	Patient Reported Outcome
Q1	First quartile

Q3	Third quartile
RNA	Ribonucleic acid
S	Spike
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SIC	Symptoms of Infection with COVID-19
Th1	Helper cell type 1
Th2	Helper cell type 2
TLF	Tables, Listings and Figures
TNF-α / TNF-a	Tumor necrosis factor alpha
ULOQ	Upper limit of quantification
VE	Vaccine efficacy
VNA	Virus Neutralization Assay
WHO	World Health Organization

9.2. Appendix 2 Changes to Protocol-Planned Analyses

9.3. Appendix 3 Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

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 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or 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.

** 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.

10. REFERENCES