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 16

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).

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

Confidentiality Statement

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 16	This Document
Amendment 15	7 October 2021
Amendment 14	29 July 2021
Amendment 13	04 June 2021
Amendment 12	27 May 2021
Amendment 11	6 May 2021
Amendment 10	25 February 2021
Amendment 9	18 December 2020
Amendment 8	08 December 2020
Amendment 7	03 November 2020
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 16 (This Document)

Overall Rationale for the Amendment: The main purpose of this amendment is to remove planned Ad26.COV2.S booster vaccinations at 24 months after the primary regimen for Cohort 2 participants, due to the smaller number of participants remaining than expected, mostly related to severe acute respiratory syndrome (coronavirus-2SARS-CoV-2) infections and receiving authorized/licensed coronavirus disease-2019 (COVID-19) vaccines outside of the study. The primary analysis was completed. Operational challenges have impacted the feasibility of a strict follow-up of any COVID-19 episode and active follow-up cannot be sustained. Therefore, the protocol has been amended to reduce the number of on-site visits and to change the requirements for reporting new COVID-19 episode by applying a passive follow-up approach. There will be no changes to the safety follow-up of serious adverse events (SAEs) and adverse events of special interest (AESIs).

Additionally, changes included in the Belgium-specific Amendment 15 are now included in this global amendment. These include changes requested by the Federal Agency for Medicines and Health Products (FAMHP) to restrict the Ad26.COV2.S booster vaccine administration to participants ≥65 years of age. Also, reference to the thrombosis with thrombocytopenia syndrome (TTS) case definition was updated, and reference was made to the approval by EMA of the Ad26.COV2.S booster posology.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.3 Cohort 2a 1.3.4 Cohort 2b 3 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5.5 Criteria for Temporarily Delaying Administration of Study Vaccination 6 Study Vaccination and Concomitant Therapy	Text was added to indicate that participants in Cohort 2 will no longer be offered Ad26.COV2.S booster vaccination at 24 months after completion of their primary regimen, as initially planned.	Cohort 2 results following booster vaccination at 24 months removed due to the smaller number of participants remaining than expected, mostly related to SARS-CoV-2 infections and receiving authorized/licensed COVID-19 vaccines outside of the study

Section Number and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Vaccination 8 Study Assessments and Procedures		
1.2 Schema 1.3.10 Procedures for Participants Receiving an Ad Hoc Booster Vaccination of $5x10^{10}$ vp Ad26.COV2.S Table 9	Text was added to clarify that participants, who did not complete Booster FU2 visit before local approval of protocol Amendment 16, will attend Booster FU2 visit as their last visit, as scheduled in the Schedule of Activities. Text was added to clarify that participants who had completed Booster FU2 visit before the local approval of protocol Amendment 16 will attend an on-site last visit within 6 weeks (+7 days) from the local approval of protocol Amendment 16, for reconsenting and safety follow-up.	There is no placebo comparison for the ad hoc booster vaccination group, due to unblinding and offered open-label ad hoc booster vaccination to participants. Moreover, the post-booster safety and immunogenicity follow-up are explored in larger Phase 3 studies.
1.1 Synopsis 1.3.6.1 Passive Follow-up (As of Local Approval of Protocol Amendment 16) 4.1 Overall Design 8.1.2.1 Passive Follow-up (As of Amendment 16) 8.1.3 Procedures in Case of Asymptomatic COVID-19 RT-PCR Confirmed Infection 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Text was updated to indicate that the management of new suspected COVID-19 episodes has been changed from active to passive follow-up, defined as safety follow-up on-site visits to document COVID-19 events as (S)AEs.	Constant evolution of the COVID-19 pandemic has impacted the practical implementation of a strict follow-up of new suspected COVID-19 episodes.
1.1 Synopsis 1.3.10 Procedures for Participants Receiving an Ad Hoc Booster Vaccination of $5x10^{10}$ vp Ad26.COV2.S 3 Objectives and Endpoints 4.1 Overall Design 4.4 End of Study Definition 5 STUDY POPULATION 5.2 Exclusion Criteria 5.5 Criteria for Temporarily Delaying Administration of Study Vaccination 6.1 Study Vaccinations Administered 6.3 Measures to Minimize Bias: Randomization and Blinding 7.1 Discontinuation of Study Vaccination	Text was added to specify that in Belgium, the booster vaccination with Ad26.COV2.S will only be offered to participants ≥65 years of age	Based on FAMHP feedback

Section Number and Name	Description of Change	Brief Rationale
7.5 Discontinue form Cohort Vaccination 8 Study Assessments and Procedures - Table 9 8.3.5 Pregnancy 8.7 Assessments and Procedures after Protocol Amendment 15 Approval (Ad Hoc Booster Vaccination)		
1.2 Schema 1.3.3.2 Booster Vaccination Cohort 2a 1.3.4.2 Booster Vaccination Cohort 2b 8 STUDY ASSESSMENTS AND PROCEDURES Table 6 Table 7	Text was updated to indicate that Visits 12, 13, and 14-15 (Cohort 2a) and Visits 15, 16 and 17-18 (Cohort 2b) have been removed. Footnotes were added to Schema Cohort 2a and Cohort 2b, Schedule of Activities for booster vaccination for Cohort 2a and 2b. Text in Tables 6 and 7 was updated to indicate that Visit 11 will be the last visit for Cohort 2a and Visit 14 will be the last visit for Cohort 2b, and that no vaccination will be offered at these visits and only safety assessment will be performed.	Clarification. Safety and immunogenicity follow-up visits; Visits 12, 13, and 14-15 (Cohort 2a) and Visits 15, 16 and 17-18 (Cohort 2b), respectively, are no longer applicable, as no booster will be given at Visit 11 (Cohort 2a) and Visit 14 (Cohort 2b).
4.4 End of Study Definition	The last scheduled visit for Cohort 2 participants will be at 24 months after completion of the primary regimen.	As booster vaccinations at 24 months after completion of the primary regimen will not be administered to Cohort 2 participants, the timing of the final scheduled visit for such participants has been updated.
10.4.3 Severity Criteria	The AESI definition of thrombocytopenia has been updated based on the Brighton Collaboration definition.	To align across the Ad26.COV2.S program.
1.1 Synopsis 11 REFERENCES	The reference to the Brighton Collaboration case definition of thrombotic events and thrombocytopenia was updated.	Update
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Addition of minor clarifications.

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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) and AESIs from the first vaccination until 2 years 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 and AESIs until the end of the study • Following Amendment 16, booster vaccination at 24 months will not be performed

• 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). • Analysis of antibodies binding to SARS-CoV-2 S protein and the receptor-binding domain (RBD) of the SARS-CoV-2 S protein by Meso Scale Discovery (MSD) assay • 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. • Analysis of neutralizing and binding antibodies against emerging SARS-CoV-2 virus lineages. 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).

Objectives	Endpoints
• 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
• 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
• To explore the immune responses in fine needle lymph node aspirations (LNAs) in Cohort 1b participants	• Magnitude, phenotype, antigen specificity and subset distribution of immune and stromal cells in lymph nodes and peripheral blood • Molecular network analysis of functional regulation of T- and B-cell subsets in lymph nodes

* Excluding Group 5 (placebo only) participants who received a single dose of 5×10^{10} vp Ad26.COV2.S at the time of unblinding, after Emergency Use Authorization (EUA) or approval in any country and local approval of protocol Amendment 10.

Hypothesis

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

Ad Hoc Booster Vaccination

Following local approval of protocol Amendment 15, the following objectives are applicable for all eligible participants who consent to receive a single ad hoc booster dose of $5x10^{10}$ vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. See study design section below for more details.

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26.COV2.S at the 5×10^{10} vp dose level administered as ad hoc booster vaccination in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	• Solicited local and systemic AEs for 7 days after ad hoc booster vaccination. • Unsolicited AEs for 28 days after ad hoc booster vaccination. • SAEs and AESIs from ad hoc booster vaccination until the end of the study.
Secondary	
• To obtain samples to evaluate potential thromboembolic events following ad hoc booster vaccination by obtaining platelet counts and sufficient extra sera for specialized studies at the day of booster vaccination and 28 days later.	• Platelet count on the day of ad hoc booster vaccination and 28 days after ad hoc booster vaccination. Additional analysis on collected sera samples in case of potential thromboembolic events.
Exploratory	
• To assess the humoral and cellular immune response to Ad26.COV2.S ad hoc booster dose.	<u>Humoral immune response assessment may include, and is not limited to:</u> • 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]) against the original strain and emerging variants. • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S and RBD protein from the original strain and emerging variants. • Adenovirus neutralization. • Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping). • Epitope-specificity characterization for B- and T cells. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. <u>In a subset of participants, cellular immune response assessment may include, and is not limited to:</u> • Th1 and Th2 immune responses as assessed by flow cytometry after SARS-CoV-2 S protein peptide stimulation of PBMCs and ICS including CD4+/CD8+, IFNγ, IL-2,

Objectives	Endpoints
	TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.
• 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

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.

Following Emergency Use Authorization (EUA), conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is locally approved by the Health Authority and Independent Ethics Committees (IEC)/Institutional Review Board (IRB), will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo only will be offered a single dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in the placebo groups.

Following local approval of protocol Amendment 15, all ongoing eligible participants will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Participants who choose to receive an outside of the study booster vaccination with the Ad26.COV2.S vaccine (if recommended by local authorities and available) or another authorized COVID-19 vaccine, choose not to receive an ad hoc booster vaccination, or are not eligible to receive the ad hoc booster vaccination, will not be withdrawn from the study and will be encouraged to remain in the study.

The following ongoing participants will not be eligible to receive this ad hoc booster vaccination:

- Group 5 participants (all cohorts) who crossed over from placebo to receive Ad26.COV2.S at the $5x10^{10}$ vp dose level (ie, placebo crossover vaccination).
- Group 5 participants (all cohorts) who did not opt for the placebo crossover vaccination and therefore have not received any vaccination with the Ad26.COV2.S vaccine.
- Cohort 2 participants who will receive a booster vaccination according to their initial schedule at 6 and 12 months after the primary regimen (Groups 2 and 3, respectively).

- Applicable to Belgium only: Per the Belgian-specific protocol Amendment 15, participants aged <65 years enrolled at Belgian sites.

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. Optional fine needle LNA will be collected from consenting participants approximately 12 months after their 2nd vaccination (active or placebo) or approximately 6 months after the ad hoc crossover vaccination (for participants who crossed over from placebo to receive active Ad26.COV2.S $5x10^{10}$ vp vaccination), to further explore the immune responses in lymph nodes.

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: Vaccination Schedules[a]

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) [b]			
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)** [c]	**Day 57** [c]
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)** [c]	**Day 57 (Vaccination 2)** [c]
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. Following local approval of protocol Amendment 15, all eligible participants will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago.

b. 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.

c. 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. The immunogenicity results available from Cohort 1a supported the administration of the 2nd vaccination at Day 57 in Cohort 2b.

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.

Booster Vaccinations in Cohort 2

Note: For participants at Belgian sites: per Belgian-specific Protocol Amendment 15, this section is no longer applicable as participants aged <65 years enrolled at Belgian sites are not eligible to receive a booster vaccination with Ad26.COV2.S.

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 or12 months, after completion of the primary regimen, and will receive placebo at the other applicable time point. As a control, a subgroup of participants who received Ad26.COV2.S for the primary regimen will receive placebo at 6 months and 12 months, after completion of the primary regimen. In addition, participants who received

placebo for the primary regimen will receive placebo at 6 months and 12 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 [e] N/A per Amendment 16
1 [d]	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 [d]	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Ad26.COV2.S 5×10^{10} vp
5 [c]	15	Placebo	Placebo [c]	Placebo [c]	Placebo [c]
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 and 12 months after completion of the single-dose primary regimen.
c. At the time of unblinding, after EUA or approval in any country and local approval of Protocol Amendment 10, only the Group 5 (placebo only) participants not willing to receive a single dose of 5×10^{10} vp Ad26.COV2.S or another authorized/licensed COVID-19 vaccine will continue Group 5 booster vaccinations in Cohort 2a.
d. Applicable to the US only: Following local approval of Protocol Amendment 15, all participants of Groups 1 and 4 not willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will continue booster vaccinations in Cohort 2a according to their current schedule.
e. Following local approval of Protocol Amendment 16, booster vaccinations (either placebo or Ad26.COV2.S $5x10^{10}$ vp) will not be administered at 24 months after completion of the primary regimen.

EUA = Emergency Use Authorization; N = number of participants; N/A = not applicable; 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 [e] N/A per Amendment 16
1 [d]	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 [d]	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 [c]	15	Placebo	Placebo	Placebo [c]	Placebo [c]	Placebo [c]
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 and 12 months after completion of the 2-dose primary regimen. If the 2nd vaccination at Day 57 is not provided, then participants will discontinue the study.
c. At the time of unblinding, after EUA or approval in any country and local approval of Protocol Amendment 10, only the Group 5 (placebo only) participants not willing to receive a single dose of 5×10^{10} vp Ad26.COV2.S or another authorized/licensed COVID-19 vaccine will continue Group 5 booster vaccinations in Cohort 2b.
d. Applicable to the US only: Following local approval of Protocol Amendment 15, all participants of Groups 1 and 4 not willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will continue booster vaccinations in Cohort 2b according to their current schedule.
e. Following local approval of Protocol Amendment 16, booster vaccinations (either placebo or Ad26.COV2.S $5x10^{10}$ vp) will not be administered at 26 months after completion of the primary regimen.

EUA = Emergency Use Authorization; N = number of participants; N/A = not applicable; vac = vaccination; vp = virus particles.

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

Passive Follow-up (As of local approval of Protocol Amendment 16)

As of Amendment 16, active follow-up of suspected COVID-19 episodes will be replaced by a passive follow-up approach. New suspected COVID-19 episodes will be participant-reported and may include available laboratory findings from testing outside the clinical study. Site staff will collect information on the new COVID-19 episodes at scheduled visits and report these as SAEs, or AEs, as applicable. Participants may also contact the site at any time in between scheduled visits to report a safety concern (eg, hospitalization) or COVID-19 episodes. Concomitant therapies related to these events are to be reported, as well as any confirmatory COVID-19 laboratory information, if available. Some participants may have an ongoing COVID-19 episode at time of local approval of Protocol Amendment 16. Also, under Protocol Amendment 16, the SIC will no longer be completed. Hence, participants with an ongoing COVID-19 episode will stop completing the SIC as of local approval of Protocol Amendment 16. The outstanding activities planned for the follow-up of COVID-19 episodes will also end on that date for the participants (eg, no further samples and no further visit in the context of the COVID-19 follow-up).

Active Follow-up (Prior to local approval of Protocol Amendment 16)

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. Following local approval of protocol Amendment 15, participants will not be required to complete the booklet but will be contacted by the site regularly to check whether they experienced 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 or until sign and symptom resolution, whichever comes first. Long-term sequelae of COVID-19 (eg, anosmia, headache, fatigue, and other symptoms at the investigator's judgement) will not be followed until their resolution if not resolved within a month.
- 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 sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

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, unless they withdraw consent from the study. The participant will be followed until resolution of clinical symptoms (except for long-term sequelae of COVID-19).

Procedures in Case of Asymptomatic COVID-19 RT-PCR Confirmed Infection

Passive Follow-up (As of local approval of Protocol Amendment 16)

- Participants will report any positive RT-PCR SARS-CoV-2 test results during their scheduled visit.

Active Follow-up (Prior to local approval of Protocol Amendment 16)

For each cohort, if participants receive a positive SARS-CoV-2 result from a private/off-study test, without experiencing any COVID-19 symptoms, the following should take place:

- Participants should contact the study site at the time the positive RT-PCR SARS-CoV-2 test result is obtained.
- The study staff should ensure the participant's medical care provider has been/will be informed. The sponsor recommends to contact the participant at least once per week, and recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

In the event a participant experiences COVID-19-like signs or symptoms after obtaining a positive RT-PCR SARS-CoV-2 test result, procedures as described above should be followed with the exception of nasal swab collection to assess the presence of SARS-CoV-2 infection or influenza infection.

The above must be done in accordance with local country and site level recommendations for COVID-19, and these participants will not be permitted to receive further study vaccination administrations. The participant can continue in the study for safety and immunogenicity assessments, unless they withdraw consent from the study.

Assessments and Procedures after Emergency Use Authorization (EUA) or Approval in any Country

Procedures installed at the time of unblinding all participants after EUA or approval in any country and local approval of protocol Amendment 10, will also apply to participants who were unblinded at their own request prior to Amendment 10.

All currently enrolled participants will be contacted by the study site to inform them whether they received active vaccine or placebo only. Participants will be counseled regarding the importance to continue practicing preventative measures to limit the spread of the disease including social distancing, wearing face masks, and frequent hand washing, in compliance with local and national guidelines. This contact will be documented in the source documents.

Participants in the active vaccine groups will be informed they received at a minimum the dose level approved for Emergency Use (single-dose regimen of $5x10^{10}$ vp Ad26.COV2.S), and will be asked to continue to be followed in this study in line with the Schedule of Activities (SoA). Participants who were unblinded (at any time) and did not receive an authorized/licensed COVID-19 vaccine outside of the study, will be permitted to receive the Cohort 2 booster vaccinations. If they opt to receive an authorized/licensed COVID-19 vaccine outside of the study, they will be discontinued from further study vaccination[a].

Participants who received placebo only during primary regimen and who are still actively enrolled in the study, will be offered a single dose of 5×10^{10} vp Ad26.COV2.S (ie, placebo crossover vaccination). If willing to receive, they will discontinue from participation in the placebo groups and will be redirected to the SoA "Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S (Placebo Crossover Vaccination) after EUA or Approval in any Country". If they opt to receive an authorized/licensed COVID-19 vaccine outside of the study, they will discontinue the study. If they choose not to receive any additional vaccinations, they will be asked to continue to be followed in this study in line with the SoA.

Assessments and Procedures after Protocol Amendment 15 Approval (Ad Hoc Booster Vaccination)

Following local approval of protocol Amendment 15, all eligible participants will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S.

As soon as possible, but no later than 120 days post local approval of protocol amendment 15, the ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago.

The following ongoing participants will not be eligible to receive this ad hoc booster vaccination:

- Group 5 participants (all cohorts) who crossed over from placebo to receive Ad26.COV2.S at the $5x10^{10}$ vp dose level (ie, placebo crossover vaccination).
- Group 5 participants (all cohorts) who did not opt for the placebo crossover vaccination and therefore have not received any vaccination with the Ad26.COV2.S vaccine.

[a] Following local approval of protocol Amendment 15, participants who received an authorized/licensed COVID-19 vaccine outside of the study are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.

- Cohort 2 participants who will receive a booster vaccination according to their initial schedule at 6 and 12 months after the primary regimen (Groups 2 and 3, respectively).
- Applicable to Belgium only: Per the Belgian-specific protocol Amendment 15, participants aged <65 years enrolled at Belgian sites.

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, and dosed at 5×10^{10} vp and 1×10^{11} vp
- Placebo: 0.9% NaCl solution

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

For participants who received placebo only during primary regimen and who are offered a single dose of 5×10^{10} vp Ad26.COV2.S at the time of unblinding (ie, after Emergency Use Authorization or approval in any country and local Amendment 10 approval), a dose level of 5×10^{10} vp in a volume of 0.5 mL will be administered.

Following local approval of protocol Amendment 15, for all eligible participants who are offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S, a dose level of 5×10^{10} vp in a volume of 0.5 mL will be administered.

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 tables.

Optional exploratory assessments on lymph node samples for Cohort 1b (Beth Israel Deaconess Medical Center [BIDMC]) may include, but are not limited to characterization of resident immune cells by flow cytometry, gene expression, and cytokine release.

Summary of Immunogenicity Assays Used for the Double-blind Phase and Post Unblinding of the Study

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 binding antibodies to S protein (MSD)	Analysis of antibodies binding to SARS-CoV-2 S protein and the RBD of SARS-CoV-2 S protein
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other lineage), 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

Assay	Purpose
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
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)
Evaluation of germinal centers in lymph nodes	Analysis of the immune responses in lymph nodes

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

Summary of Immunogenicity Assays Used for the Ad Hoc Booster Vaccination

Assay	Purpose
Humoral Immunogenicity	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein from the original strain and/or emerging variants
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S and RBD protein from the original strain and/or emerging variants
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein
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
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

ELISA = enzyme-linked immunosorbent assay; ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; RBD = receptor-binding domain; 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 15 minutes to 1 hour depending on the vaccination being administered (see SoAs for details) 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.

For all cohorts, 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. Adverse events of special interest (AESI) will be reported from local approval of protocol Amendment 11 until the end of the study/early withdrawal.

For enrolled participants who received placebo only during primary regimen and who are accepting a single dose of 5×10^{10} vp Ad26.COV2.S offered at the time of unblinding (ie, after Emergency Use Authorization (EUA) or approval in any country and local approval of protocol Amendment 10), different procedures apply. A single dose of 5×10^{10} vp Ad26.COV2.S will be administered during an ad hoc crossover visit and participants will remain under observation at the study site for at least 15 minutes following vaccination. SAEs, special reporting situations (whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products), and COVID-19-like signs and symptoms will be reported from the time of unblinding until the end-of-safety-follow-up phone call. In addition, suspected AESIs will be reported after local approval of protocol Amendment 11 is obtained.

From the time of local approval of protocol Amendment 11 onwards, TTS is considered an AESI. Suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below 150,000/μL[a]]) will be reported until the end of the study/early withdrawal. An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS.

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

[a] Updated Proposed Brighton Collaboration process for developing a standard case definition for study of new clinical syndrome X, as applied to Thrombosis with Thrombocytopenia Syndrome (TTS). 11 November 2021. https://brightoncollaboration.us/wp-content/uploads/2021/11/TTS Updated-Brighton-Collaboration-Case-Defintion-Draft-Nov-11-2021.pdf. Accessed: 25 February 2022.

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[a]: 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 from 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.

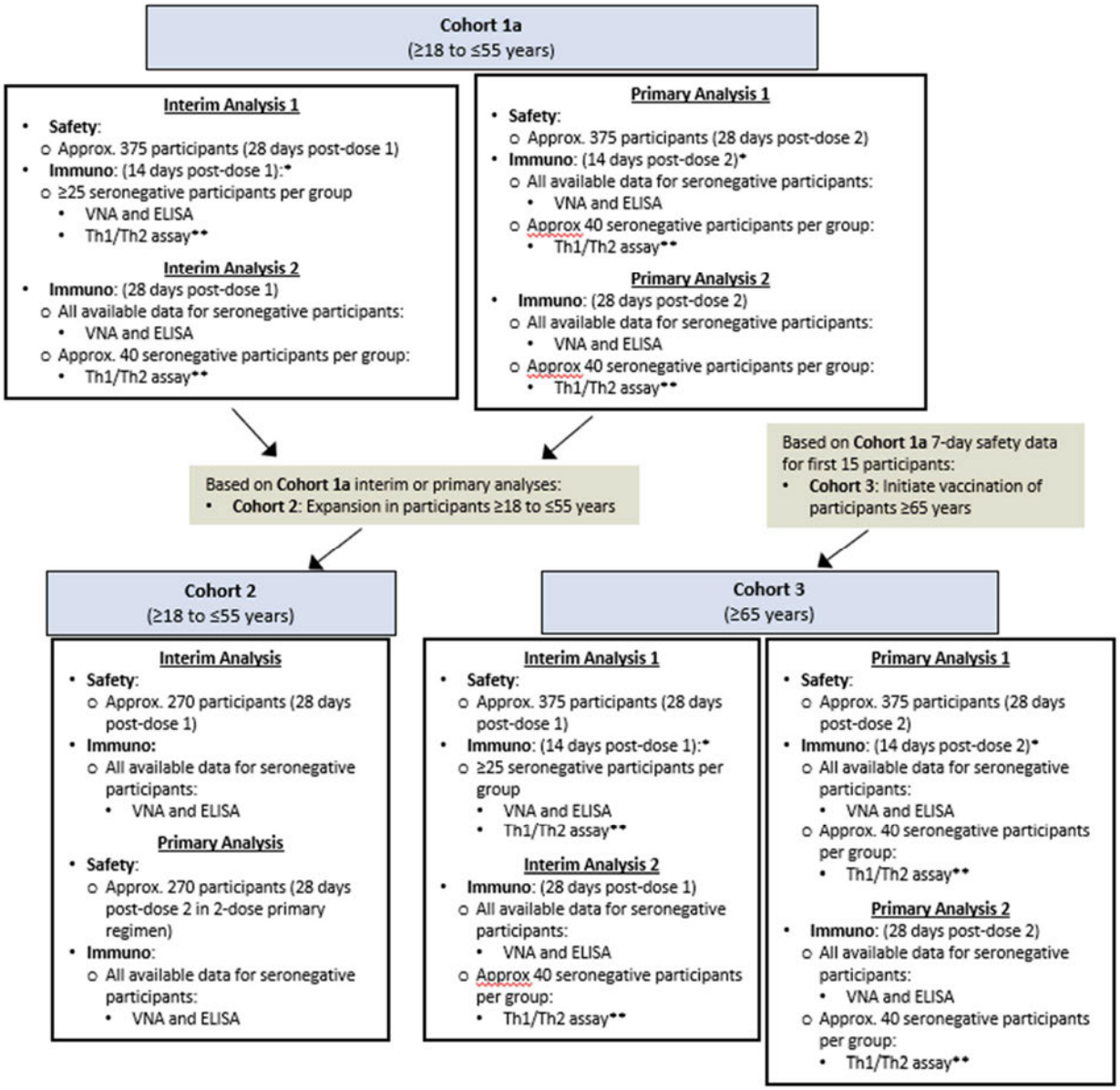
The immunogenicity analyses will be performed on the PPI population. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols).

Planned Analyses

Interim and primary analyses for each cohort are presented in the figure below. Additional interim analyses may be conducted by the sponsor as needed.

[a] If a participant would be vaccinated out of window due to a study pause (per Section 6.9), this will not by default be a reason for excluding this participant from the PPI. A sensitivity analysis might also be performed. Further details will be described in the Statistical Analysis Plan.

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 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 the study earlier.

Analyses for Participants Requesting Unblinding in Order to Receive an Authorized/Licensed COVID-19 Vaccine

Investigators may receive requests to unblind study participants who become eligible to receive an authorized/licensed COVID-19 vaccine if/when these become available. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorized/licensed vaccine according to local immunization guidelines or recommendations and if the

participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures. The reason for the unblinding request should be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see body of the protocol for more details).

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no clinical data on the safety of receiving a different COVID-19 vaccine after receiving Ad26.COV2.S. In the event of participant unblinding to obtain an authorized/licensed COVID-19 vaccine and the participant received an authorized/licensed COVID-19 vaccine outside of the study, no further study vaccination will be permitted[a]. Unblinded participants, whether in the vaccine or control group that did not receive an authorized/licensed COVID-19 vaccine outside of the study will be asked to continue to be followed in this study in line with the schedule of activities to the extent that they permit, including Cohort 2 booster vaccinations. Safety and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. The statistical analyses will follow the same approach as outlined below.

Analyses after Unblinding all Participants Following Emergency Use Authorization (EUA) or Approval in any Country

In general, after unblinding, participants who received placebo only during primary regimen, can elect to receive a single dose of 5×10^{10} vp Ad26.COV2.S offered at the study site, can opt to receive an authorized/licensed COVID-19 vaccine outside of the study, or may choose not to receive any additional vaccinations. Participants who received active vaccine will be asked to continue the study or can opt to receive an authorized/licensed COVID-19 vaccine outside of the study.

The participants in cohorts 1a, 1b, and 3 have completed the planned study vaccination regimen by the time of unblinding (or have discontinued earlier). Participants in Cohorts 2a and 2b will not have completed the planned vaccination schedule by the time of unblinding, because the booster vaccinations will not yet have occurred.

The safety and efficacy analyses will be censored at the date of unblinding or the receipt of an unscheduled vaccine[b], whichever event occurs first. SAEs reported after unblinding or receipt of an unscheduled vaccine, whichever comes first, will be listed.

The immunogenicity analyses will be censored at the date of the receipt of an unscheduled vaccine. Immunogenicity samples taken after the receipt of an unscheduled vaccine will be included in the listings and flagged.

Analyses pertaining to the booster vaccinations in Cohorts 2a and 2b will be produced as planned. Post-booster safety or efficacy analyses will not include participants who were unblinded at their own request, nor participants who received an unscheduled vaccination.

[a] Following local approval of protocol Amendment 15, participants who received an authorized/licensed COVID-19 vaccine outside of the study are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.

[b] Unscheduled vaccine: for placebo participants: a single dose of 5×10^{10} vp Ad26.COV2.S offered at the study site or an authorized/licensed COVID-19 vaccine offered outside of the study; for participants in the active vaccine groups: an authorized/licensed COVID-19 vaccine offered outside of the study.

The analysis strategy is depicted graphically in the figure below.

Analysis After Receipt of the Ad Hoc Booster Vaccination

Amendment 15 of this protocol offers eligible study participants a single ad hoc booster vaccination with the Ad26.COV2.S vaccine at the 5×10^{10} vp dose level. The main analyses will be conducted as described above, in which censoring is applied for the various statistical analyses depending on the date of unblinding or receipt of an unscheduled vaccine. In addition, receipt of the ad hoc booster vaccination will also be a reason for censoring data from the main analyses.

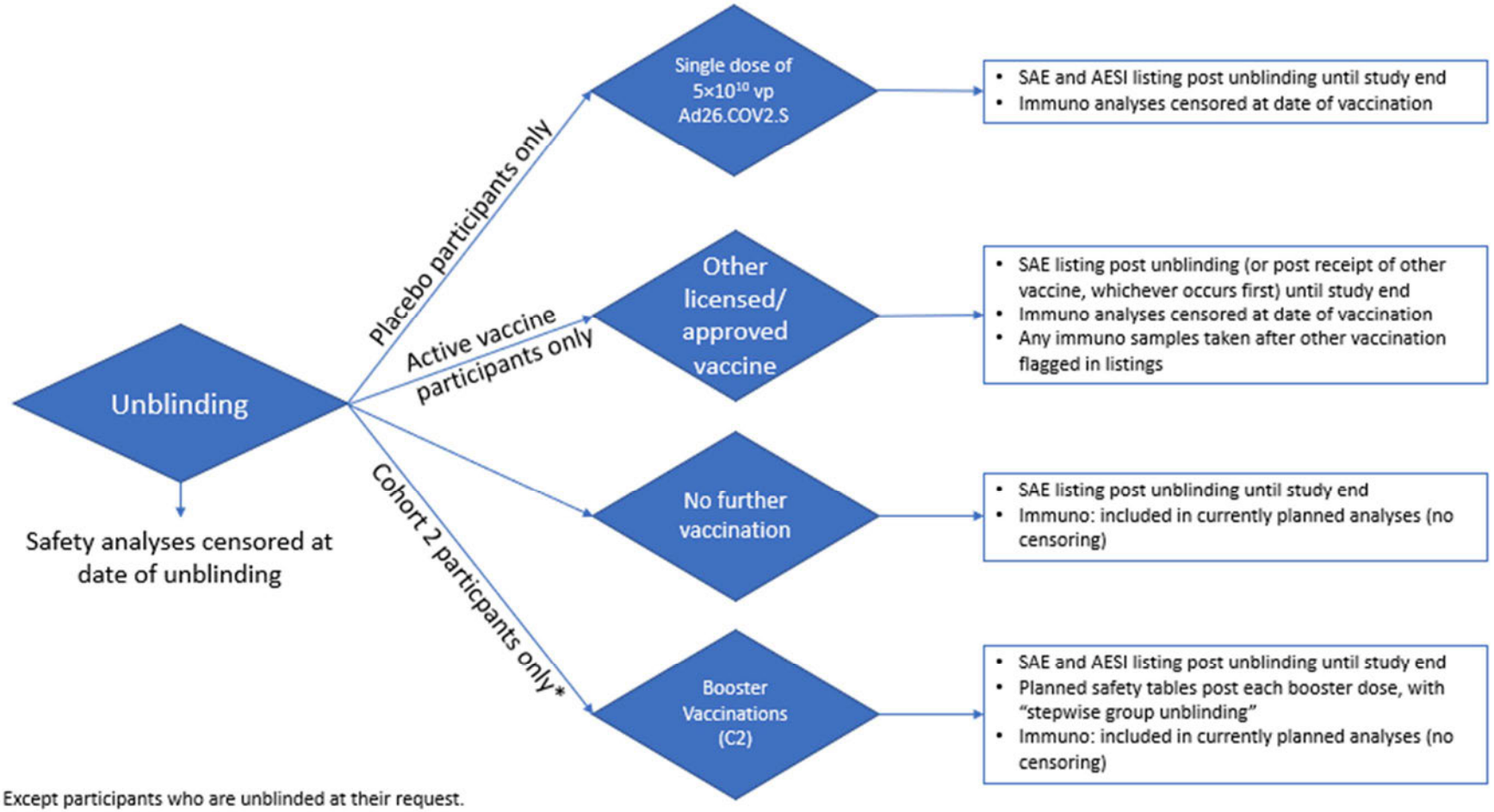
For safety and reactogenicity, additional analyses will be conducted on study participants who received the ad hoc booster vaccination. Safety and reactogenicity analyses will be presented from the start of the ad hoc booster vaccination until 7 days post vaccination for reactogenicity, until 28 days post vaccination for unsolicited AEs, and until the end of the study for SAEs and AESIs.

For immunogenicity, an additional analysis will be conducted on study participants who received the ad hoc booster vaccination. Immunogenicity analyses will be presented from the start of the ad hoc booster vaccination and will show their immune responses at each subsequent time point, as available.

The analyses will be descriptive, presenting study participants according to their original vaccination regimen. In addition, the analyses may also be conducted separately by subgroups of study participants who received a COVID-19 vaccine outside of the study versus study participants who did not receive a COVID-19 vaccine outside of the study. Additional exploratory analyses may be conducted.

Details for the analysis of the ad hoc booster vaccination will be provided in an amendment to the study Statistical Analysis Plan.

Figure: Analysis strategy after unblinding, depicted by scenario



AESI = adverse event of special interest; C = cohort; SAE = serious adverse event

1.2. Schema

Figure 1: Schematic Overview of Cohort 1a

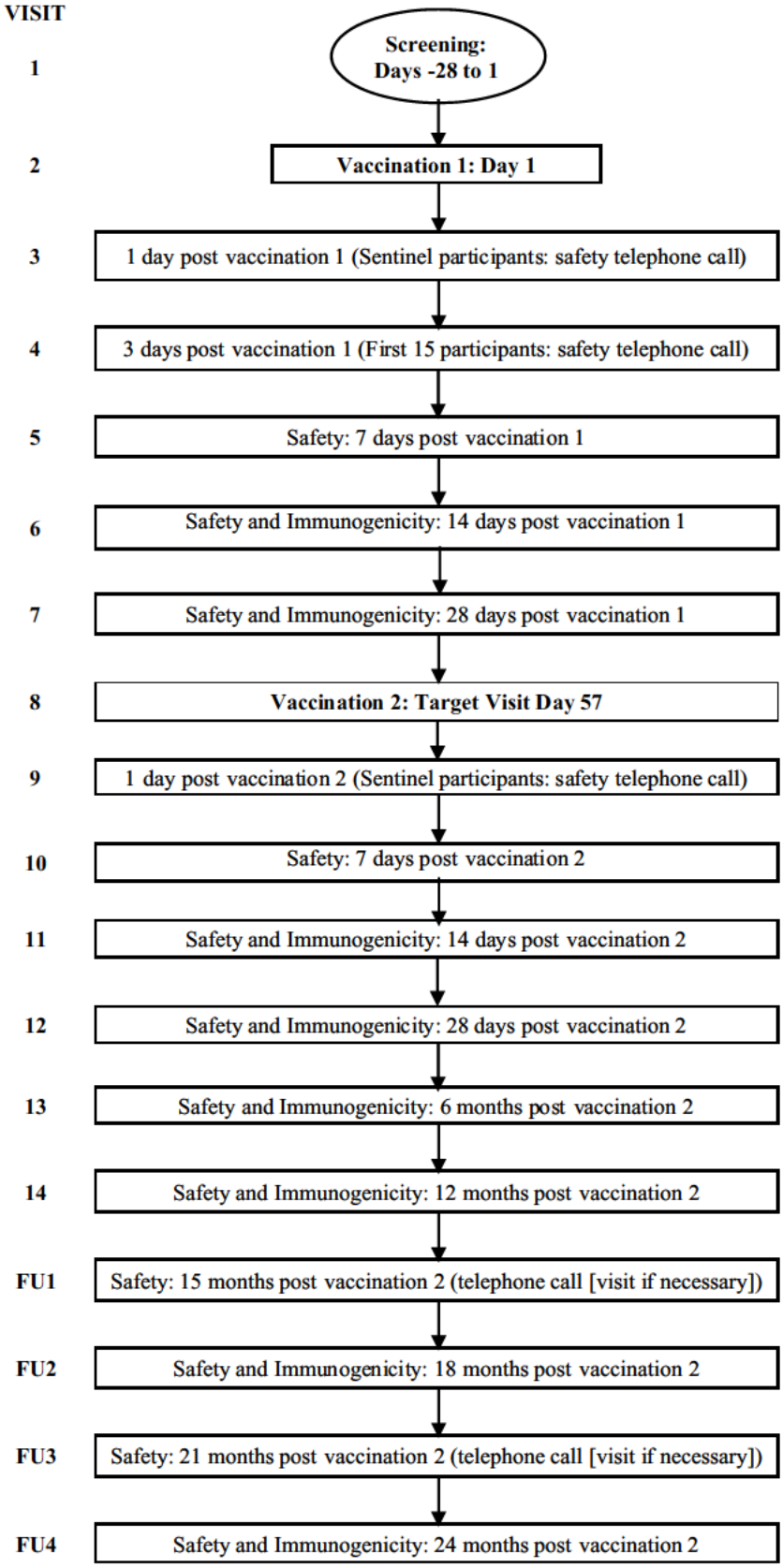
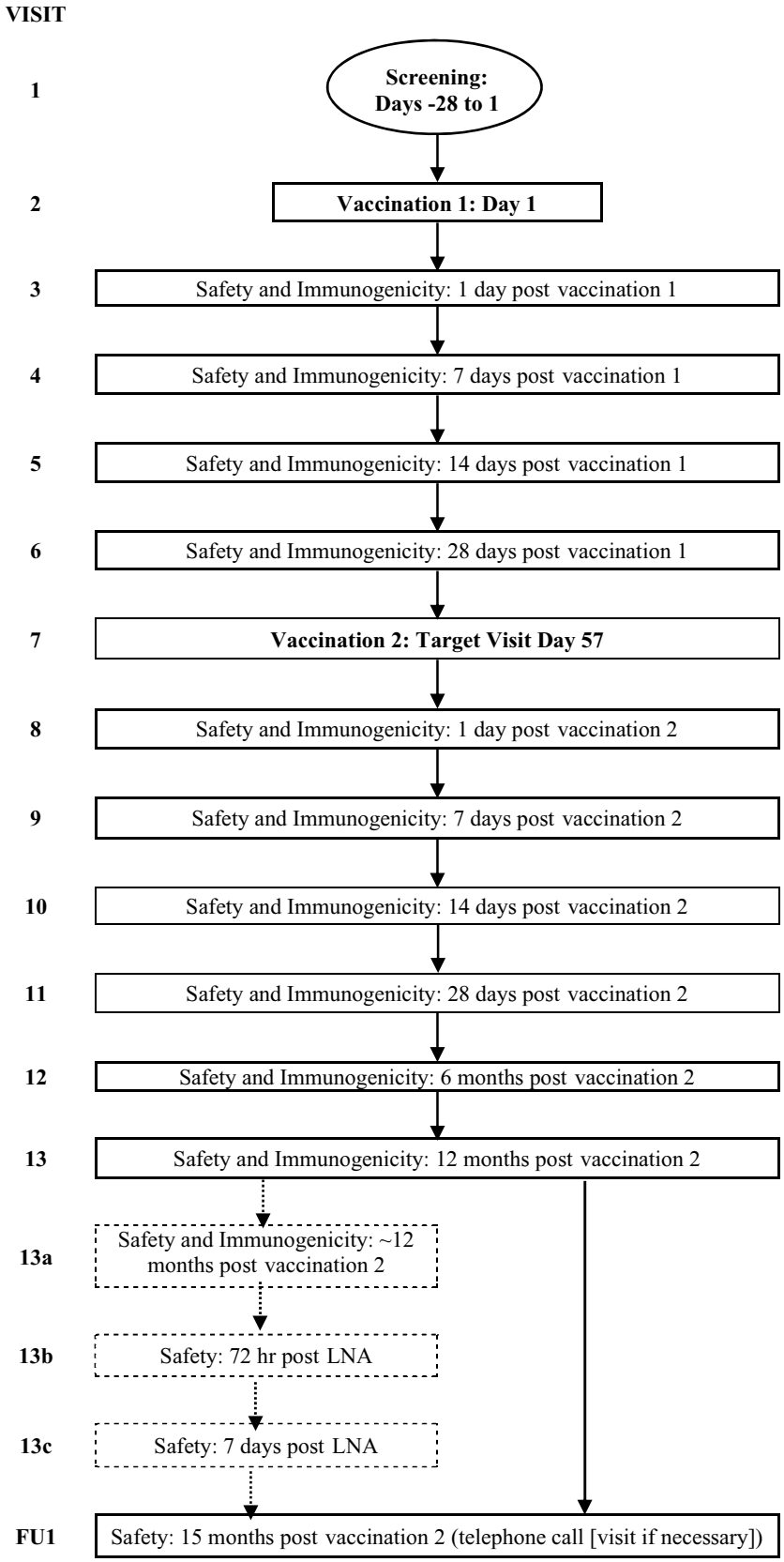


Figure 2: Schematic Overview of Cohort 1b



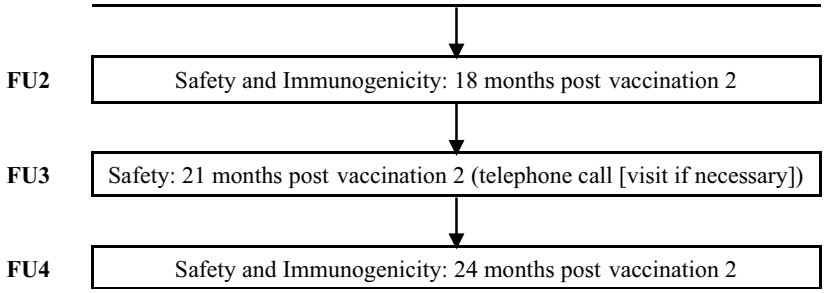
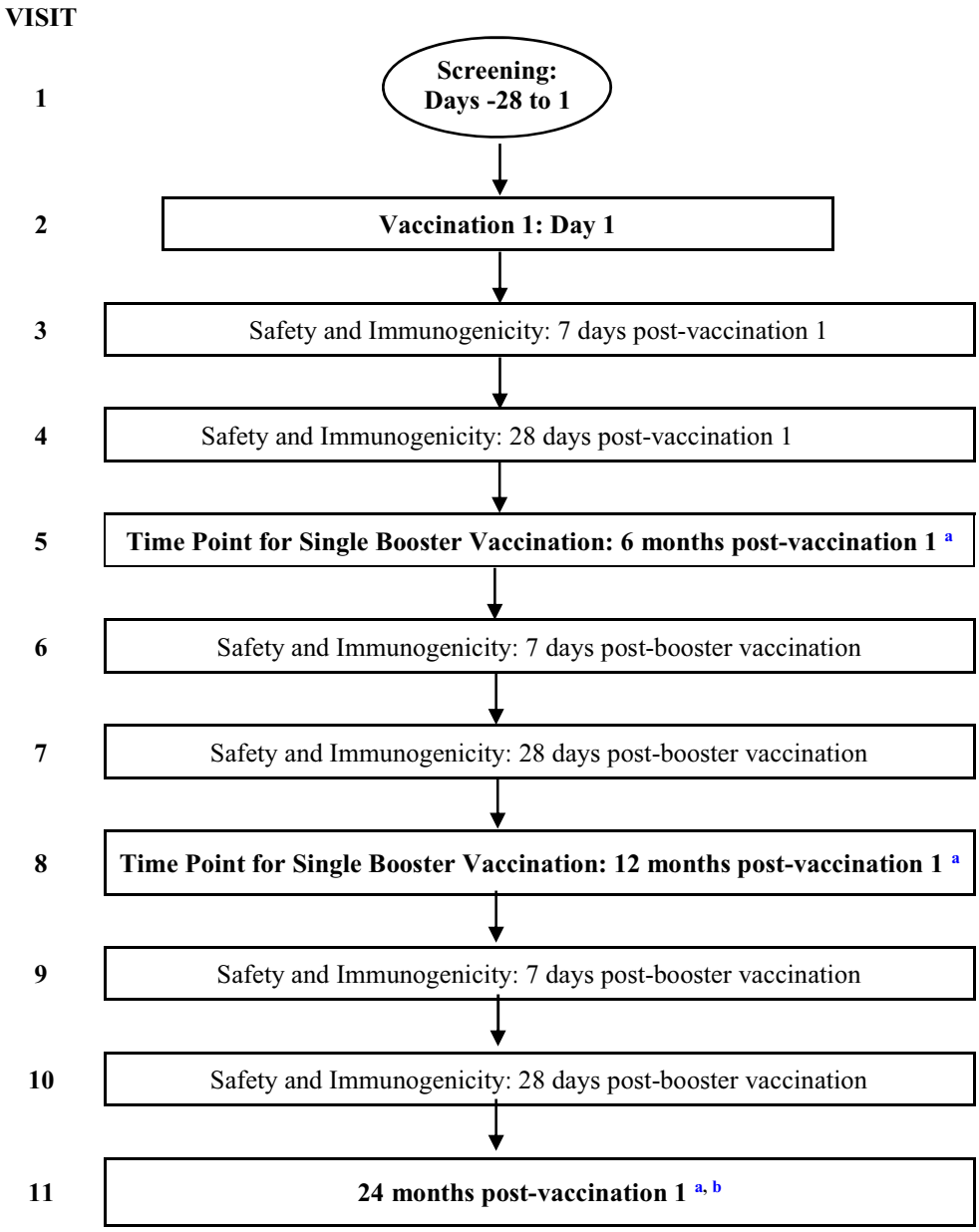

FU2
Safety and Immunogenicity: 18 months post vaccination 2
FU3
Safety: 21 months post vaccination 2 (telephone call [visit if necessary])
FU4
Safety and Immunogenicity: 24 months post vaccination 2

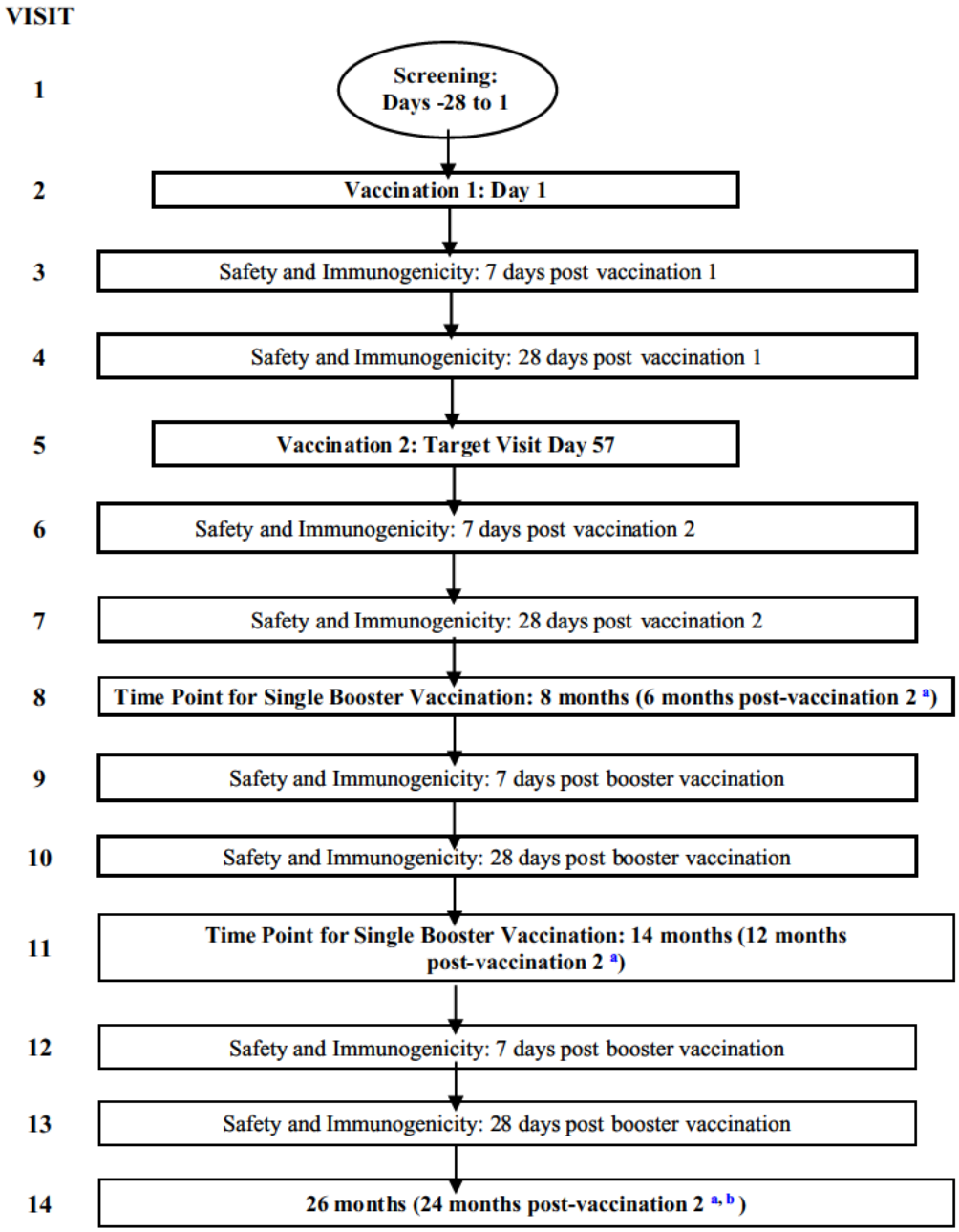
Figure 3: Schematic Overview of Cohort 2a



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

b. Visit 11 is the last visit.

Figure 4: Schematic Overview of Cohort 2b



a. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 8 months or 14 months (ie, 6 months or 12 months after completion of the 2 dose primary regimen) and will receive placebo at the other applicable timepoint. If the 2nd vaccination at Day 57 is not provided, then participants will discontinue the study (refer to Section 7.2). Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 3 for further details.

b. Visit 14 is the last visit.

Figure 5: Schematic Overview of Cohort 3

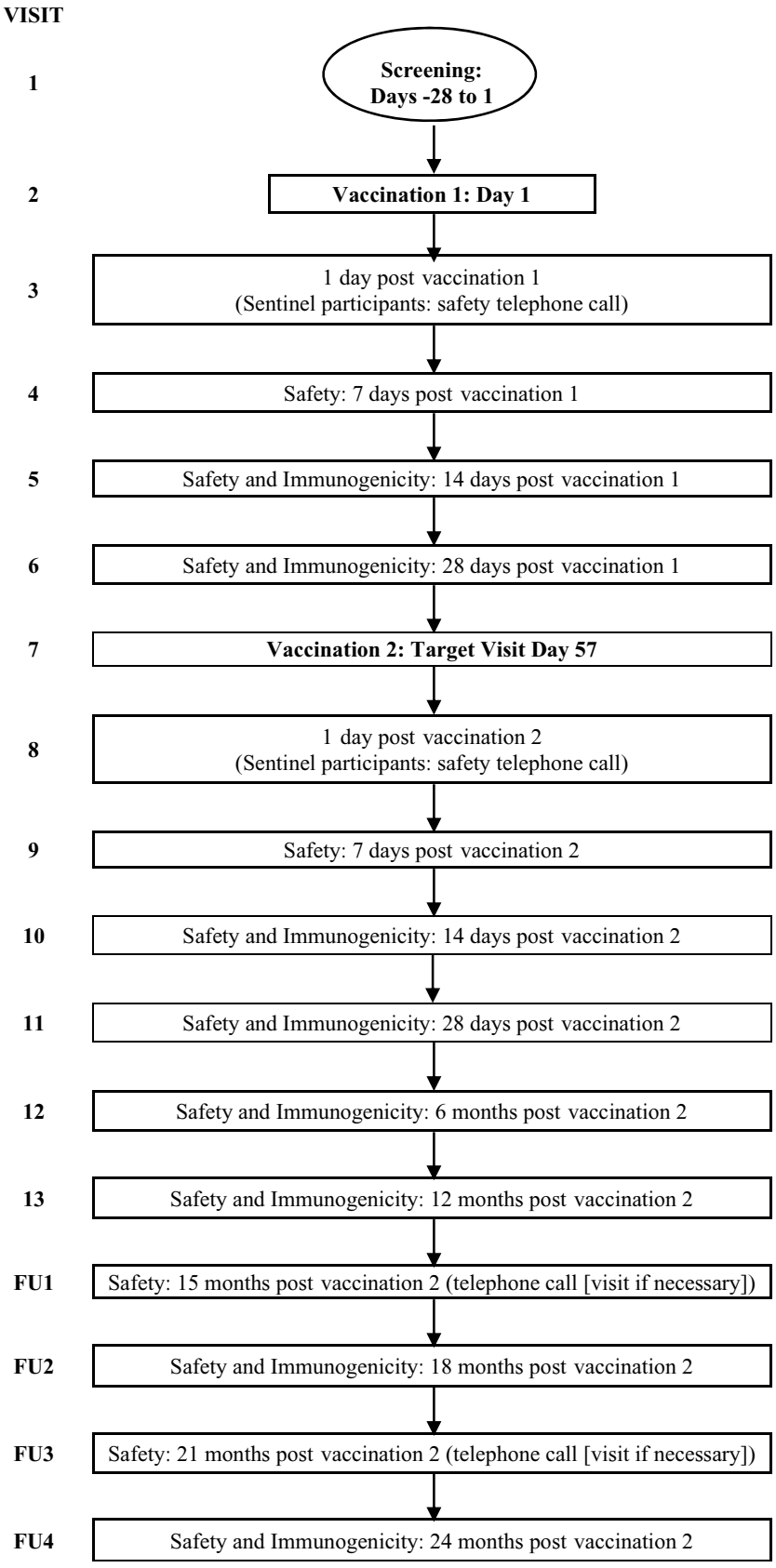
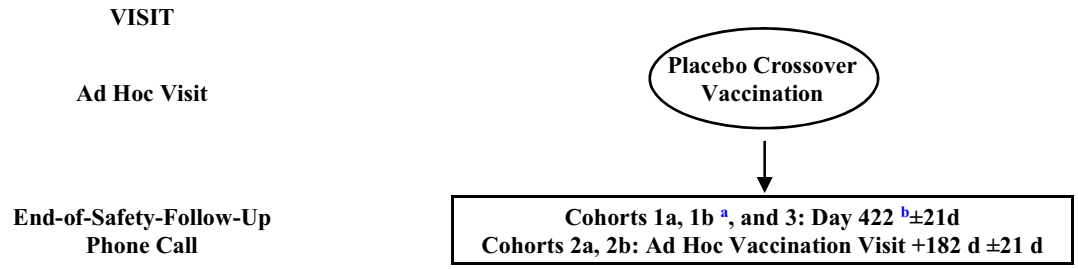


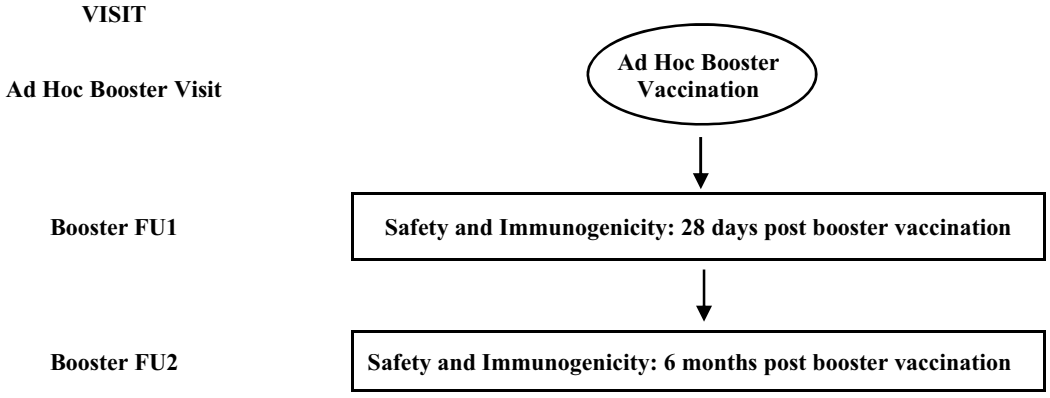
Figure 6: Schematic Overview of Placebo Crossover Vaccination



a. At this visit, optional fine needle LNA procedure will be performed on Cohort 1b participants who have provided consent. In this case, the visit will take place onsite instead of a telephone call. This onsite visit will not be the final visit, as there will be 2 other follow-up visits (see Section 1.3.2.1).

b. Or ad hoc vaccination visit +182 d ± 21 d, whichever comes first. Day 422 was the initially planned study completion date (based on the participant's initial SoA).

Figure 7: Schematic Overview of Ad Hoc Booster Vaccination



1.3. Schedule of Activities (SoA)

1.3.1. Cohort 1a

Participants who consent for the additional follow-up will follow the additional procedures as specified in Section 1.3.9. Participants who consent for the ad hoc booster vaccination will discontinue from the current schedule and follow the procedures as specified in Section 1.3.10. If not willing to do the additional follow-up or receive the ad hoc booster vaccination, they will continue to follow the assessments according to the schedule below.

Phase	**Screening** [a]	**Study Period** [b]													
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, l] incl. body temperature	●	❷			●	●	●	❷		●	●	●			❹
Nasal swab sample	❼	❽													
Serological test for SARS CoV 2 specific antibodies	●	❽													
Randomization		❶													
Pre vaccination 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

Phase	Screening [a]	Study Period [b]													
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
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/AESI recording [n]		----- *Continuous*-----													●
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, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see section 7.2) 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1). For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.

AE = adverse event; AESI = adverse event of special interest; 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; SoA = schedule of activities; tel = telephone contact; vac = vaccination.

1.3.2. Cohort 1b

Participants who consent for the additional follow-up will follow the additional procedures as specified in Section 1.3.9. Participants who consent for the ad hoc booster vaccination will discontinue from the current schedule and follow the procedures as specified in Section 1.3.10. If not willing to do the additional follow-up or receive the ad hoc booster vaccination, they will continue to follow the assessments according to the schedule below.

Phase	Screening [a]	Study Period [b]												
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 [d]	
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 [e]	●													
Inclusion/exclusion criteria	●	❶												
Demographics	●													
Medical history/prestudy meds	●	●												
Physical examination [f]	●													
Vital signs [g, j] incl. body temperature	●	❷	●	●	●	●	❷	●	●	●	●			❹
Nasal swab sample	❻	❼												
Serological test for SARS CoV 2 specific antibodies	●	❼												
Randomization		❶												
Pre vaccination symptoms [h]		❶					❶							
Urine pregnancy test [i]	●	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 [j]		●					●							

Phase	Screening [a]	Study Period [b]												
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 [d]	
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
Solicited AE recording		----- *Continuous*-----			❹		----- *Continuous*-----							❹
Unsolicited AE recording [k]		----- *Continuous through +28 d*-----					❺							❺
SAE/AESI recording [l]		----- *Continuous*-----												●
Concomitant meds [m]		----- *Continuous*-----												●
Participant diary distribution [n]		●					●							
Participant diary review [o]			●	●				●	●					
Training and distribution: nasal swab kit and symptom surveillance booklet		●												
Signs and symptoms surveillance [p]		----- *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, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see section 7.2) 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. For schedule of activities of the optional lymph node aspiration (LNA) procedure in Cohort 1b participants (Beth Israel Deaconess Medical Center [BIDMC]), see Section 1.3.2.1 for more details.

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 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.
i. For women of childbearing potential only.
j. 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.
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 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1). For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.
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 1.3.6.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; LNA = lymph node aspirate; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SoA = schedule of activities; vac = vaccination.

1.3.2.1. Optional Lymph Node Aspirates for Cohort 1b Participants (Beth Israel Deaconess Medical Center [BIDMC])

Phase	LNA Follow-up Period		
Visit #	13a	13b	13c
Visit Timing	Vac 2 + 12 mo	LNA + 72 hr	LNA + 7 d
Target Visit Day ±Window	422*-21 d/+60 d	425±1 d	429±1 d
Visit Type	**Safety & Immuno**	**Safety (Telephone contact)**	**Safety**
Written informed consent for optional LNA	●		
LNA procedure [a]	●		
Follow up phone call [b]		●	
AE recording [c]	●	●	●
SAE/AESIs recording [d]	●	●	●
Concomitant meds [e]	●	●	●

* The lymph node aspirate procedure may occur at Day 422 (in this case Visit 13 and optional Visit 13a will coincide) or will be performed at a later timepoint during the LNA follow-up period.

a. The LNA procedure might be scheduled a few days after the ICF signature for logistical preparations of the LNA procedure at the site. However, the subsequent visits (13b, 13c) should be calculated based on the day of the LNA procedure and not based on the day of the ICF signature.

b. Study site staff will contact the participant by phone within 72 hours after the procedure. Study staff will coordinate if the participant prefers to schedule an in person visit for the follow up contact. The participant will be asked questions regarding any ongoing bleeding, pain control, and signs or symptoms of infection. Participants contacted by a study coordinator will be asked if they would like to speak with a study clinician to review their health status.

c. AEs and special reporting situations that are related to the optional lymph node aspirate procedure 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 optional study/early withdrawal.

d. 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1).

e. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations that are relevant to AEs related to the LNA procedure, as well as any SAEs and AESIs must be recorded.

AE = adverse event; AESI = adverse event of special interest; d = day(s); hr = hour; ICF = informed consent form; LNA = lymph node aspirate; mo = months; SAE = serious adverse event; Vac = vaccination.

1.3.3. Cohort 2a

1.3.3.1. Primary Regimen Cohort 2a

Phase	Screening [a]	Study Period [b]			
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, k] incl. body temperature	●	❷	●	●	❹
Nasal swab sample	❻	❼			
Serological test for SARS CoV 2 specific antibodies	●	❼			
Randomization [s]		❶			
Pre vaccination 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	❸ 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/AESI recording [n]		*- Continuous- - - - - - - - - - - - - - - - - - - -*			●
Concomitant meds [o]		*- Continuous- - - - - - - - - - - - - - - - - - - -*			●
Participant diary distribution [p]		●			
Participant diary review [q]			●		

Phase	Screening [a]	Study Period [b]			
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, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards. (see Section 8.3.1). For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.
s. Vaccination and randomization may be done on the same day.

AE = adverse event; AESI = adverse event of special interest; 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; SoA = schedule of activities; vac = vaccination.

1.3.3.2. Booster Vaccination Cohort 2a

Participants from Groups 1 and 4 who consent for the ad hoc booster vaccination will discontinue from the current schedule and follow the procedures as specified in Section 1.3.10. If not willing to receive the ad hoc booster vaccination, they will continue to follow the assessments according to the schedule below.

Phase	Study Period [b]							
Visit #	5	6	7	8	9	10	11[p]	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	
Target Visit Day ±Window	183±21	190*±2 [b]	211*±3	366±21	373*±2 [b]	394*±3	731±21	
Visit Type	Booster [c]	Safety and Immuno		Booster [c]	Safety and Immuno		Safety	Early Exit
Vital signs [d, i] incl. body temperature	❷	●	●	❷	●	●		❺
Pre vaccination symptoms [e]	❶			❶				
Urine pregnancy test [f]	❶			❶				
Humoral immunity (serum), mL	❶ 30	● 30	● 30	❶ 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			❼ 2.5
Blood sample, mL [h]	❶ 7			❶ 7				
Vaccination	●			●				
1 hour post vaccination observation [i]	●			●				
Solicited AE recording [j]	*Cont +7d*			*Cont +7d*				❺
Unsolicited AE recording [k]	*- - - - Continuous through +28 d- - - -*			*- - - - Continuous through +28 d- - -*				❻
SAE/AESI recording [l]	*- Continuous- -*							●
Concomitant meds [m]	*- Continuous- -*							●
Participant diary distribution	●			●				
Participant diary review [n]		●			●			
Signs and symptoms surveillance [o]	*- - - - - - - - - - - - Continuous- - - - - - - - - -*							
Approx. daily blood draw, mL: Participants at selected sites [g] [Other participants]	37 [37]	32.5 [30]	30 [30]	97 [37]	32.5 [30]	30 [30]		82.5 [20]

Phase	Study Period [b]							
Visit #	5	6	7	8	9	10	11[p]	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	
Target Visit Day ±Window	183±21	190*±2 [b]	211*±3	366±21	373*±2 [b]	394*±3	731±21	
Visit Type	Booster [c]	Safety and Immuno		Booster [c]	Safety and Immuno		Safety	Early Exit
Approx. cumulative blood draw, mL: Participants at selected sites [g] [Other participants]	292.5 [159.5]	325 [189.5]	355 [219.5]	452 [256.5]	484.5 [286.5]	514.5 [316.5]		-

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 11 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 11, but for whom consent is not withdrawn, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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, 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.
c. Participants designated to receive a single booster vaccination will receive Ad26.COV2.S at 6 months or 12 months after completion of the primary regimen and will receive placebo at the other applicable time point. Participants not designated to receive a single booster vaccination will receive placebo at each applicable time point. 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. A blood sample will be used for a platelet count (as part of a complete blood count if applicable) in a local laboratory. A Serum sample will be stored for potential future coagulation-related testing in a central laboratory if the participant experiences a suspected AESI (see Section 10.2.2, Appendix 2). If the blood and serum samples have been taken within 5 days before vaccination, and platelet results are available, sample collection does not need to be repeated before vaccination.

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. 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 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1). For schedule of activities related to AESI, see Section for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.
n. If an event is still ongoing on Day 190, or Day 373, 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.
p. Following local approval of Protocol Amendment 16, participants will have on-site Visit 11 as scheduled. Visit 11 will be the last visit for Cohort 2a, at which only safety evaluations will be performed.

AE = adverse event; AESI = adverse event of special interest; 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 Cohort 2b

Phase	Screening [a]			Study Period [b]				
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, k] incl. body temperature	●	❷	●	●	❷	●	●	❹
Nasal swab sample	❻	❼						
Serological test for SARS CoV 2 specific antibodies	●	❼						
Randomization [s]		❶						
Pre vaccination 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/AESI recording [n]		*- - - - - - - - - - Continuous- - - - - - - - - -*						●
Concomitant meds [o]		*- - - - - - - - - - Continuous- - - - - - - - - -*						●
Participant diary distribution [p]		●			●			
Participant diary review [q]			●			●		

Phase	Screening [a]			Study Period [b]				
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, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1). For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.
s. Vaccination and randomization may be done on the same day.

AE = adverse event; AESI = adverse event of special interest; 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; SoA = schedule of activities; vac = vaccination

1.3.4.2. Booster Vaccination Cohort 2b

Participants from Groups 1 and 4 who consent for the ad hoc booster vaccination will discontinue from the current schedule and follow the procedures as specified in Section 1.3.10. If not willing to receive the ad hoc booster vaccination, they will continue to follow the assessments according to the schedule below.

Phase	Study Period [b]							
Visit #	8	9	10	11	12	13	14[p]	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	
Target Visit Day ±Window	239*±21	246*±2 [b]	267*±3	422*±21	429*±2 [b]	450*±3	787*±21	
Visit Type	Booster [c]	Safety and Immuno		Booster [c]	Safety and Immuno		Safety	Early Exit
Vital signs [d, i] incl. body temperature	❷	●	●	❷	●	●		❺
Pre vaccination symptoms [e]	❶			❶				
Urine pregnancy test [f]	❶			❶				
Humoral immunity (serum), mL	❶ 30	● 30	● 30	❶ 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			❼ 2.5
Blood sample, mL [h]	❶ 7			❶ 7				
Vaccination	●			●				
1 hour post vaccination observation [i]	●			●				
Solicited AE recording [j]	*Cont +7d*			*Cont +7d*				❺
Unsolicited AE recording [k]	*- - - - Continuous through +28 d- - - -*			*- - - - Continuous through +28 d- - - -*				❻
SAE/AESI recording [l]	*- - - - Continuous- - - -*							●
Concomitant meds [m]	*- - - - Continuous- - - -*							●
Participant diary distribution	●			●				
Participant diary review [n]		●			●			

Phase	Study Period [b]							
Visit #	8	9	10	11	12	13	14[p]	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	
Target Visit Day ±Window	239*±21	246*±2 [b]	267*±3	422*±21	429*±2 [b]	450*±3	787*±21	
Visit Type	Booster [c]	Safety and Immuno		Booster [c]	Safety and Immuno		Safety	Early Exit
Signs and symptoms surveillance [o]	---------- *Continuous* ----------							
Approx. daily blood draw, mL: Participants at selected sites [g] [Other participants]	37 [37]	32.5 [30]	30 [30]	97 [37]	32.5 [30]	30 [30]		82.5 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [g] [Other participants]	530.5 [270]	563 [300]	593 [330]	690 [367]	722.5 [397]	752.5 [427]		

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 14 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 14, but for whom consent is not withdrawn, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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, 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 or 12 months after completion of the 2-dose primary regimen and will receive placebo at the other applicable time point. If the 2nd vaccination at Day 57 is not provided, then participants will discontinue the study (refer to Section 7.2). 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. A blood sample will be used for a platelet count (as part of a complete blood count if applicable) in a local laboratory. A serum sample will be stored for potential future coagulation-related testing in a central laboratory if the participant experiences a suspected AESI (see Section 10.2.2, Appendix 2). If the blood and serum samples have been taken within 5 days before vaccination and platelet results are available, sample collection does not need to be repeated before vaccination.
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. 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 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1. For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.
n. If an event is still ongoing on Day 246, or Day 429, 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.
p. Following local approval of Protocol Amendment 16, participants will have on-site Visit 14 as scheduled. Visit 14 will be the last visit for Cohort 2b, at which only safety evaluations will be performed.

AE = adverse event; AESI = adverse event of special interest; 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

Participants who consent for the additional follow-up will follow the additional procedures as specified in Section 1.3.9. Participants who consent for the ad hoc booster vaccination will discontinue from the current schedule and follow the procedures as specified in Section 1.3.10. If not willing to do the additional follow-up or receive the ad hoc booster vaccination, they will continue to follow the assessments according to the schedule below.

Phase	Screening [a]	Study Period [b]												
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, k] incl. body temperature	●	❷		●	●	●	❷		●	●	●			❹
Nasal swab sample	❼	❽												
Serological test for SARS CoV 2 specific antibodies	●	❽												
Randomization		❶												
Pre vaccination 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]		●					●							

Phase	Screening [a]	Study Period [b]												
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
Solicited AE recording		----- *Continuous*-----					----- *Continuous*-----							❹
Unsolicited AE recording [l]		----- *Continuous through +28 d*-----					----- *Continuous through +28 d*-----							❺
SAE/AESI recording [m]		----- *Continuous*-----												●
Concomitant meds [n]		----- *Continuous*-----												●
Participant diary distribution [o]		●					●							
Participant diary review [p]			❻	●				❻	●					
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, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1). For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.

AE = adverse event; AESI = adverse event of special interest; 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; SoA = schedule of activities; tel = telephone contact; vac = vaccination

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

1.3.6.1. Passive Follow-up (As of Local Approval of Protocol Amendment 16)

As of Amendment 16, active follow-up of suspected COVID-19 episodes will be replaced by a passive follow-up approach. New suspected COVID-19 episodes will be participant-reported and may include available laboratory findings from testing outside the clinical study. Site staff will collect information on the new COVID-19 episodes at scheduled visits and report these as SAEs, or AEs, as applicable. Participants may also contact the site at any time in between scheduled visits to report a safety concern (eg, hospitalization) or COVID-19 episodes. Concomitant therapies related to these events are to be reported, as well as any confirmatory COVID-19 laboratory information, if available. Guidance on (S)AE coding may be provided. Some participants may have an ongoing COVID-19 episode at time of local approval of Protocol Amendment 16. Also, under Protocol Amendment 16, the SIC will no longer be completed. Hence, participants with an ongoing COVID-19 episode will stop completing the SIC as of local approval of Protocol Amendment 16. The outstanding activities planned for the follow-up of COVID-19 episodes will also end on that date for the participants (eg, no further samples and no further visit in the context of the COVID-19 follow-up).

1.3.6.2. Active Follow-up (Prior to Local Approval of Protocol Amendment 16)

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 or until sign and symptom resolution, whichever comes first. Long-term sequelae of COVID-19 (eg, anosmia, headache, fatigue, and other symptoms at the investigator's judgement) will not be followed until their resolution if not resolved within a month.

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 8.1.2.3, 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. The sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

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

1.3.7. Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S (Placebo Crossover Vaccination) after EUA or Approval in any Country

Visit	Ad Hoc Visit	End-of-Safety-Follow-Up Phone Call
Visit Timing ±Window		Cohorts 1a, 1b [a], and 3: Day 422*±21d Cohorts 2a, 2b: Ad Hoc Vaccination Visit +182 d ±21 d
Informed reconsent [b]	●	
Urine pregnancy test [c]	❶	
Blood sample, mL(approx.) [d]	❶ 7	
Vaccination [e]	●	
15-minutes post-vaccination observation [f]	●	
SAE/AESI recording [g]	----------*Continuous*----------	
Recording of COVID-19-like signs and symptoms [h]	----------*Continuous*----------	

❶ pre vaccination

* or ad hoc vaccination visit +182 d ± 21 d, whichever comes first. Day 422 was the initially planned study completion date (based on the participant's initial SoA).

a. At this visit, optional fine needle LNA procedure will be performed on Cohort 1b participants (Beth Israel Deaconess Medical Center [BIDMC]) who have provided consent. In this case, the visit will take place onsite instead of a telephone call. This onsite visit will not be the final visit, as there will be 2 other follow-up visits (see Section 1.3.2.1).

b. Signing of the ICF should be done before any visit-related procedure.

c. For women of childbearing potential in Cohort 1 and 2 only.

d. A blood sample will be used for a platelet count (as part of a complete blood count if applicable) in a local laboratory. A serum sample will be stored for potential future coagulation-related testing in a central laboratory if the participant experiences a suspected AESI (see Section 10.2.2, Appendix 2). If the blood and serum samples have been taken within 5 days before vaccination, and platelet results are available, sample collection does not need to be repeated before vaccination.

e. Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is locally approved by the Health Authority and IEC/IRB will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo only, will be offered a single dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in the placebo groups (refer to Sections 7.4 and 8.6).

f. Participants will be closely observed for a minimum of 15 minutes post-vaccination for the presence of any acute reactions following vaccination.

g. SAEs 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 of unblinding until the end-of-safety-follow-up phone call/early withdrawal. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1).

h. Continued recording of signs and symptoms of COVID-19 until the end-of-safety-follow-up. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6.

AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); EUA = emergency use authorization; LNA = lymph node aspirate; SAE = serious adverse event; SoA = schedule of activities.

1.3.8. Procedures for Participants with a Suspected AESI

The medical management of thrombotic events with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, from the American Society of Hematology[3], British Society of Haematology - Expert Haematology Panel[10], and the CDC[15]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended. Management of the participant should not be delayed by decision-making of the AESI Adjudication Committee. In the event of a suspected thrombotic event, thrombocytopenia or TTS, laboratory assessments (to be performed locally) are required to facilitate diagnosis and determine treatment options, including but not limited to platelet count and anti-platelet factor 4 (anti-PF4) tests.

Additional blood samples should be collected for central laboratory testing as detailed below. However, results of central laboratory testing may not be available to guide immediate treatment decisions.

Timing relative to onset of suspected AESI	**AESI Day 1** [a]	**AESI Day 29** [b]
Visit Window		**±7 d**
Site to report AESI [c]	●	
Blood samples, mL (approx.) [d]	● 15	● 15
TTS AESI form [e]	*- - - - Continuous- - - -*	
Concomitant therapies [f]	●	●

a. Day 1 refers to first awareness of the event, which might be later than the date of onset. Every effort should be made to report as much information as possible about the event to the sponsor in a reasonable timeframe. The investigator should contact the sponsor for input on the feasibility of collecting blood samples, including the need for additional samples based on the nature of the event.
b. Day 29 is to be calculated relative to the actual day of onset of the event. If the event is not resolved on Day 29, subsequent follow-up assessments can be performed at unscheduled visits as needed until resolution of the event. If the event is reported to the investigator more than 28 days after the onset of the event, AESI Day 29 visit will therefore become redundant and does not need to be performed.
c. Suspected AESIs must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious AEs) or causality assessment (see Section 8.3.6).
d. On AESI Day 1 and again on Day 29, whole blood samples will be used for a platelet count (as part of a complete blood count, if applicable) in a local laboratory. Serum (3.5 mL) and plasma (1.5 mL) samples will be derived from the whole blood samples (7 mL and 3 mL, respectively) for coagulation-related testing in a central laboratory (see Section 10.2.2, Appendix 2). For the follow-up visit, the volume of blood to be collected may vary depending on the clinical evaluation of the case. Low platelet counts are to be recorded as a suspected AESI (thrombocytopenia).
e. Medical information on local case management will be collected. Upon becoming aware of the suspected AESI, study site personnel should provide information on an ongoing basis. See Section 8.3.6 and Section 10.11, Appendix 11 for further details.
f. Refer to Section 6.8 for collection and recording of concomitant therapies associated with suspected AESIs.

AESI = adverse event of special interest; CDC = Centers for Disease Control and Prevention; PF4 = platelet factor 4; TTS = thrombosis with thrombocytopenia syndrome.

1.3.9. Additional Follow-up for Cohorts 1a, 1b and 3

Participants who consent for the ad hoc booster vaccination will discontinue from the current schedule and follow the procedures as specified in Section 1.3.10. If not willing to receive the ad hoc booster vaccination, they will continue to follow the assessments according to schedule below.

Phase	Additional Follow-up Period				
Visit #	FU1	FU2	FU3	FU4	Exit [a]
Visit Timing	Vac 2 + 15 mo	Vac 2 + 18 mo	Vac 2 + 21 mo	Vac 2 + 24 mo	
Target Visit Day ±Window	513* ± 21	604* ± 21	696* ± 21	787* ±21	
Visit Type	Safety (Telephone contact [b])	Safety and Immuno	Safety (Telephone contact [b])	Safety and Immuno	Early Exit
Humoral immunity (serum), mL		● 30		● 30	❶ 20
Cellular Immunity (PBMC), mL [c]		● 60		● 60	❶ 60
SAE/AESI recording [d]	----------*Continuous*----------				●
Concomitant meds [e]	----------*Continuous*----------				●
Signs and Symptoms Surveillance [f]	----------*Continuous*----------				●
Physical examination [g]		●		●	●
Approx. daily blood draw, mL: Participants at selected sites [c] [Other participants]	0 [0]	90 [30]	0 [0]	90 [30]	80 [20]
For Cohort 1a and 3, approx. cumulative blood draw, mL: Participants at selected sites [c] [Other participants]	785 [292.5]	875 [322.5]	875 [322.5]	965 [352.5]	-
For Cohort 1b, approx. cumulative blood draw, mL	1,045	1,135	1,135	1,225	-

❶ blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw

* The timings of visits after the second 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 Follow-up visit 4 (FU4), but for whom consent is not withdrawn, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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. The telephone contact visits can be performed as site visits, if necessary.

c. For Cohort 1a and 3, samples to be taken from approximately 200 seronegative participants at selected sites. For cohort 1b, samples will be collected in all participants if feasible.

d. 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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1).

e. 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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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.

Participants who receive COVID-19 vaccines, outside of the study, should be allowed to stay in the study (if willing), however these vaccines should be recorded in the Concomitant Medications section of the eCRF.

f. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6.
g. An abbreviated, symptom-directed examination will be performed, if determined necessary by the investigator.

AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; eCRF= electronic case report form; FU = follow-up; ICF = informed consent form; mo= months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SoA = schedule of activities; vac = vaccination

1.3.10. Procedures for Participants Receiving an Ad Hoc Booster Vaccination of $5x10^{10}$ vp Ad26.COV2.S

Phase	Ad Hoc Booster Follow-up Period			
Visit #	**Ad Hoc Booster Visit (AHBV)**	**Booster FU1**	**Booster FU2** [o, p]	**Exit** [a]
Visit Timing	**≥6 mo after last COVID-19 vaccination***	**Booster + 28d**	**Booster + 6 mo**	
Visit Target Day ±Window	**As soon as possible, but no later than 120 days post local approval of protocol amendment 15**	**AHBV** + 28 d ±3**	**AHBV** + 182 d ±21**	
Visit Type	**Booster**	**Safety and Immuno**	**Safety and Immuno**	**Early Exit**
Informed reconsent [b]	●			
Vital signs [c, h] incl. body temperature	❷	●		❺
Pre vaccination symptoms [d]	❶			
Urine pregnancy test [e]	❶			
Humoral immunity (serum), mL	❶ 30	● 30	● 30	❸ 20
Cellular Immunity (PBMC), mL [f]	❶ 60	● 60	● 60	❸ 60
Blood sample, mL [g]	❶ 7	● 7		
Vaccination	●			
15 minutes post vaccination observation [h]	●			
Solicited AE recording [i]	Cont +7d			❹
Unsolicited AE recording [j]	- - - - *Continuous through +28 d*- - - -			❺
SAE/AESI 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 [f] [Other participants]	97 [37]	97 [37]	90 [30]	80 [20]
Approx. cumulative blood draw, mL: Participants at selected sites [f] [Other participants]	97 [37]	194 [74]	284 [104]	

❶ pre vaccination; ❷ pre and post vaccination; ❸ blood sample 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.

* After local approval of protocol amendment 15, a single ad hoc booster vaccination with Ad26.COV2.S at the $5x10^{10}$ vp dose level will be offered to all eligible participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Eligibility criteria to receive the ad hoc booster vaccination are described in Section 8.7.

** The timings of visits after the ad hoc 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 Booster follow-up visit 2 (Booster FU2), but for whom consent is not withdrawn, who are not lost to follow-up, or who have not died, an early exit visit will be conducted as soon as possible. Participants who discontinue study vaccination for reasons listed in Section 7.1, will be offered all safety and immunogenicity follow-up visits according to the current SoA. Participants who wish to withdraw consent from participation in the study (see Section 7.2) 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. Signing of the ICF should be done before any visit-related procedure.
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 are recommended 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 9). 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.
e. For women of childbearing potential in Cohorts 1 and 2 only. Applicable to the US only: Participants who are pregnant may receive ad hoc booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus (see Section 8.7).
f. For Cohort 1a and 3, samples to be taken from approximately 200 seronegative participants at selected sites. For cohort 1b, samples will be collected in all participants if feasible. For cohorts 2a and 2b, samples will be collected from 27 seronegative participants at selected sites.
g. Whole blood samples will be used for a complete blood count, including platelets, in a local laboratory. Serum samples will be derived from the whole blood sample and stored for potential future coagulation-related testing in a central laboratory if the participant experiences a suspected AESI (see Section 10.2.2, Appendix 2). If the blood and serum samples have been taken within 5 days before vaccination, and platelet results are available, sample collection does not need to be repeated before vaccination.
h. Participants will be closely observed for a minimum of 15 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 15 minutes post-vaccination observation period is complete.
i. Participants will record solicited symptoms in a diary for 7 days post-vaccination. If an event is still ongoing 7 days post-vaccination, the participant should collect information until resolution.
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. Suspected AESIs are to be reported from the time of local approval of protocol Amendment 11 onwards (see Section 8.3.1). For schedule of activities related to AESI, see Section 1.3.8 for more details.
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. Receipt of a licensed/authorized COVID-19 vaccine must be recorded at any timepoint during the study. The name and

date(s) of administration of the COVID-19 vaccine should be recorded. 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. The participants should keep the diary and bring it to the study site for review of solicited signs and symptoms after vaccination by the investigator at the next visit.

n. If a participant develops COVID-19-like signs and symptoms, refer to Section 1.3.6.

o. Participants receiving the ad hoc booster who did not complete Booster FU2 visit before local approval of Protocol Amendment 16 will attend the Booster FU2 visit as per the SoA. This will be their last visit and they will be reconsented for updated safety follow-up and removal of Booster FU3 visit.

p. Participants who have already completed Booster FU2 visit before local approval of protocol Amendment 16 will attend on-site last visit within 6 weeks (+7 days) from approval of protocol amendment 16. The following assessments will be performed at this last visit: reconsenting and safety follow-up.

AE = adverse event; AESI = adverse event of special interest; AHBV = ad hoc booster visit; Cont = continuous; COVID-19 = coronavirus disease-2019; d = day(s); FU = follow-up; ICF = informed consent form; mo= months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SoA = schedule of activities

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.[31]

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.[18,54] 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.[38,40,55] 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.[5,32,42]

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.[18,25,43] 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.[56]

2.1. Study Rationale

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[21,53] It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019.[39] 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.[39] 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.[40,53] 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.[40]

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.[50,51] As of April 29, 2020, approximately 3,170,000 cases of COVID-19 had been reported.[33]

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.[12] Severe clinical presentations have been reported in as many as 20 25% of laboratory-confirmed cases.[24] 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%).[17] 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%).[47] 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.[27] In contrast, a study of 2,143 children aged <18 years in China with laboratory-confirmed (34.1%) or suspected (65.9%) COVID-19 indicated that the clinical manifestations of the disease may be less severe in children than adults, with approximately 94% of cases being asymptomatic, mild, or moderate.[23] However, young children, particularly infants, were susceptible to severe disease, with the highest proportion of severe and critical cases by age group reported for children aged <1 year (10.6% of cases in this age group). Consistent with these findings was a study of 149,082 COVID-19 cases reported in the US.[15] 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.[40] The first known cases of severe acute respiratory syndrome (SARS) occurred in Southern China in November 2002.[52] 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.[56] 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.[16,56] 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.[16,52] The case-fatality rate of MERS-CoV infections is estimated to be 35%.[16]

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.[31]

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. Recent data generated from the ongoing clinical studies VAC31518COV1001, VAC31518COV1002, VAC31518COV2001 and VAC31518COV3001, demonstrated that a single dose of Ad26.COV2.S has an acceptable safety and reactogenicity profile and is sufficient to elicit SARS-CoV-2 neutralizing antibodies in adults ≥18 years of age, including adults ≥60 years of age.

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.[20,26,34,35] 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.[44] Vaccine-induced ERD has also been described for SARS-CoV and MERS-CoV in animal models.[45]

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.[4,5,6] 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.[31]

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 10 writing, immunogenicity and safety data were available from the ongoing clinical studies VAC31518COV1001, VAC31518COV1002, VAC31518COV2001 and VAC31518COV3001 (Section 2.2). For emerging clinical data and the most comprehensive nonclinical information regarding Ad26.COV2.S, refer to the latest version of the IB and its addenda (if applicable).[31]

Sites should advice participants that side effects include fever as well as injection site pain, headache, fatigue, myalgia, and nausea 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.

Anaphylaxis is considered an important identified risk for Ad26.COV2.S. Individuals should be observed by a healthcare provider after vaccination per protocol requirements. Refer to the latest version of the IB and its addenda (if applicable) for further details.

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, and arterial thrombosis, in combination with thrombocytopenia. These cases occurred within the first 3 weeks following vaccination, mostly in women under 60 years of age. Thrombosis in combination with thrombocytopenia can be fatal. The exact physiology of TTS is unclear. TTS is considered an important identified risk for Ad26.COV2.S. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, and skin bruising and/or petechiae beyond the site of vaccination. The medical management of thrombosis with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, from the American Society of Hematology[3], British Society of Haematology - Expert Haematology Panel[10], and the CDC[14]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended. Management of the participant should not be delayed by decision-making of the AESI Adjudication Committee. Refer to the latest version of the IB and its addenda (if applicable) for further details. Due to the possibility of the occurrence of TTS after vaccination with

Ad26.COV2.S, additional reporting and data collection procedures have been included in the study for thrombotic events, thrombocytopenia, and TTS (see Section 8.3.6), which may facilitate diagnosis and clinical management of the event.

Guillain-Barré syndrome (GBS) is considered an important identified risk for Ad26.COV2.S. Cases of GBS following use of the Ad26.COV2.S vaccine have been reported during the 42 days following vaccination. Investigators should be alert to GBS signs and symptoms to facilitate diagnosis, to initiate adequate supportive care and treatment, and to rule out other causes. Refer to the latest version of the IB and its addenda (if applicable) for further details.

Risks Related to Ad26.COV2.S Administration after Previous Vaccination with Ad26.COV2.S

Preliminary safety data of an Ad26.COV2.S booster (5×10^{10} vp, 2.5×10^{10} vp, or 1×10^{10} vp) administered ≥6 months post-primary single-dose Ad26.COV2.S (5×10^{10} vp) vaccination are available from 244 participants (dose-level blinded data). The data indicate that the safety and reactogenicity of a second Ad26.COV2.S dose is acceptable and in line with the safety and reactogenicity observed after the first Ad26.COV2.S dose. There is no indication of increased reactogenicity upon administration of a second dose of Ad26.COV2.S and no safety concerns have been observed.

In addition, the primary analysis of study VAC31518COV3009 indicated that the safety profile of the vaccine remained consistent and was generally well-tolerated when administered as a second dose according to the study schedule (vaccinations at Day 1 and Day 57).[a]

Risks Related to Ad26.COV2.S Administration after Previous Vaccination with a Different COVID-19 Vaccine

To date, limited clinical data have not shown any safety issues when the Ad26.COV2.S vaccine is administered after previous vaccination or booster vaccination with a different COVID-19 vaccine. The overall benefit-risk balance assessment is ongoing.

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

[a] Johnson & Johnson News Release. Johnson & Johnson Announces Real-World Evidence and Phase 3 Data Confirming Strong and Long-Lasting Protection of Single-Shot COVID-19 Vaccine in the U.S. Press Release, New Brunswick, N.J., 21 September 2021. Available at: https://www.janssen.com/emea/sites/www janssen com emea/files/johnson johnson announces real-world evidence and phase 3 data confirming strong and long-lasting prote.pdf. Accessed on 28 September 2021.

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.

[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.

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 (see above risks related to Ad26.COV2.S). 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 15 minutes to 1 hour depending on the vaccination being administered (see SoAs for details) 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 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).

Applicable to the US only: Following local approval of protocol Amendment 15, participants who are pregnant may receive ad hoc booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus (See Section 8.7).

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,[2,8,22,29,30] 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. 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. 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. They 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.

Risks from Optional Lymph Node Aspiration

Most common risks and discomforts associated with fine needle LNA include swelling, pain, tenderness, bruising and soreness at the procedure site. These symptoms usually do not last long (1 to 2 days). Rare side effects include developing an infection, or damage to surrounding nerves or blood vessels.

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 efficacy, immunogenicity, and safety data to date support a favorable benefit-risk profile for Ad26.COV2.S in the proposed indication, ie, active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults ≥18 years of age. The overall benefit and risk balance for individual participants is ongoing.

Preliminary immunogenicity and safety data for a Ad26.COV2.S booster dose (5×10^{10} vp) at ≥6 months post-primary single-dose Ad26.COV2.S administration and efficacy data for a 2nd dose of Ad26.COV2.S 2-3 months post-primary single-dose Ad26.COV2.S administration support a favorable benefit-risk profile in participants who received a single dose of Ad26.COV2.S.

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 (SoA)

  After each vaccination, participants will remain at the study site for at least 15 minutes to 1 hour depending on the vaccination being administered (see SoAs for details) 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.

  From the time of local approval of protocol Amendment 11 onwards, TTS is considered an adverse event of special interest (AESI) (Section 8.3.6). Suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below $150{,}000/\mu L^{9}$]) must be reported to the sponsor within 24 hours of awareness. Suspected AESIs will be followed up as described in the Schedule of Activities in Section 1.3.8.

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.

AEs related to the optional LNA procedure will be monitored.

- 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) and adverse events of special interest (AESIs) from the first vaccination until 2 years 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 and AESIs until the end of the study • Following Amendment 16, booster vaccination at 24 months will not be performed

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). • Analysis of antibodies binding to SARS-CoV-2 S protein and the receptor-binding domain (RBD) of the SARS-CoV-2 S protein by Meso Scale Discovery (MSD) assay. • 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. • Analysis of neutralizing and binding antibodies against emerging SARS-CoV-2 virus lineages. 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).

Objectives	Endpoints
• 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
• 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
• To explore the immune responses in fine needle LNA in Cohort 1b participants	• Magnitude, phenotype, antigen specificity and subset distribution of immune and stromal cells in lymph nodes and peripheral blood • Molecular network analysis of functional regulation of T- and B-cell subsets in lymph nodes

* Excluding Group 5 (placebo only) participants who received a single dose of 5×10^{10} vp Ad26.COV2.S at the time of unblinding, after EUA or approval in any country and local approval of protocol Amendment 10.

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).

Ad Hoc Booster Vaccination

Following local approval of protocol Amendment 15, the following objectives are applicable for all eligible participants (see Section 8.7) that consent to receive a single ad hoc booster dose of $5x10^{10}$ vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago.

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26.COV2.S at the 5×10^{10} vp dose level administered as ad hoc booster vaccination in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions.	• Solicited local and systemic AEs for 7 days after ad hoc booster vaccination. • Unsolicited AEs for 28 days after ad hoc booster vaccination. • SAEs and AESIs from ad hoc booster vaccination until the end of the study.
Secondary	
• To obtain samples to evaluate potential thromboembolic events following ad hoc booster vaccination by obtaining platelet counts and sufficient extra sera for specialized studies at the day of booster vaccination and 28 days later.	• Platelet count on the day of ad hoc booster vaccination and 28 days after ad hoc booster vaccination. Additional analysis on collected sera samples in case of potential thromboembolic events.
Exploratory	
• To assess the humoral and cellular immune response to Ad26.COV2.S ad hoc booster dose.	Humoral immune response assessment may include, and is not limited to: • 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]) against the original strain and emerging variants. • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S and RBD protein from the original strain and emerging variants. • Adenovirus neutralization. • Functional and molecular antibody characterization (eg, avidity, Fc receptor interaction, antibody isotyping). • Epitope-specificity characterization for B- and T cells. • Passive transfer: Analysis of immune mediators correlating with protection against

Objectives	Endpoints
	experimental SARS-CoV-2 challenge in a suitable animal model. In a subset of participants, cellular immune response assessment may include, and is not limited to: • Th1 and Th2 immune responses as assessed by flow cytometry after SARS-CoV-2 S protein peptide stimulation of PBMCs and ICS including CD4+/CD8+, IFNγ, IL-2, TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.
• 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

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.

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.

Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is approved locally by the Health Authority and IEC/IRB will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo

only will be offered a single dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in the placebo groups. Refer to Sections 7.4 and 8.6 for more details.

Following local approval of protocol Amendment 15, all eligible participants (see Section 8.7) will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Participants who choose to receive an outside of the study booster vaccination with the Ad26.COV2.S vaccine (if recommended by local authorities and available) or another authorized COVID-19 vaccine, choose not to receive an ad hoc booster vaccination, or are not eligible to receive the ad hoc booster vaccination, will not be withdrawn from the study and will be encouraged to remain in the study. Refer to Section 8.7 for more details.

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. Optional fine needle LNA will be collected from consenting participants after their 2nd vaccination (active or placebo) or approximately 6 months after the ad hoc crossover vaccination (for participants who crossed over from placebo to receive active Ad26.COV2.S $5x10^{10}$ vp vaccination), to further explore the immune responses in lymph nodes (refer to Section 8.1.1.1 for more details).
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[a]

Group	N	Day 1 (Vaccination 1)	Day 57 (Vaccination 2)
Cohort 1a (Adults ≥18 to ≤55 years)			
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) [b]			
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)			
1-4	120	Ad26.COV2.S 5×10^{10} vp	No vaccination
5	15	Placebo	No vaccination
Cohort 2b (Adults ≥18 to ≤55 years)			
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)			
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. Following local approval of protocol Amendment 15, all eligible participants (see Section 8.7) will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago.

b. 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.

c. 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 8). A diagram of the study design is provided in Section 1.2, Schema.

With local approval of Protocol Amendment 16, active follow-up of suspected COVID-19 episodes will be replaced by passive follow-up (ie, follow-up at scheduled visits to document new COVID-19 events as SAEs or AEs and to record concomitant therapies associated with COVID-19). The assay methodology should be documented. During these site visits, the protocol-required safety information (eg, [S]AEs and AESIs 6 months after the last vaccination) is also collected. In between the scheduled visits, participants who experienced a (S)AE or AESI are encouraged to contact the study site.

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. The immunogenicity results available from Cohort 1a supported the administration of the 2nd vaccination at Day 57 in Cohort 2b.

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).

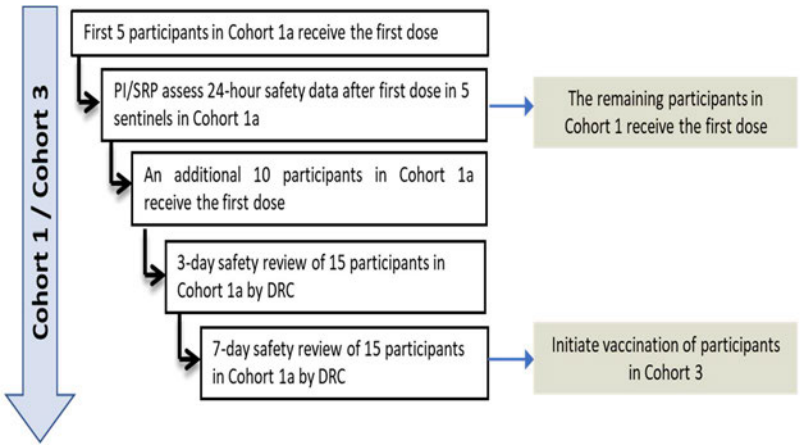
Cohort 3 (Adults Aged ≥65 Years)

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 8: 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

Booster Vaccinations in Cohort 2

Note: For participants at Belgian sites: per Belgian-specific Protocol Amendment 15, this section is no longer applicable as participants aged <65 years enrolled at Belgian sites are not eligible to receive a booster vaccination with Ad26.COV2.S.

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 or 12 months after completion of the primary regimen, and will receive placebo at the other applicable time point. As a control, a subgroup of participants who received Ad26.COV2.S for the primary regimen will receive placebo at 6 months and 12 months after completion of the primary regimen. In addition, participants who received placebo for the primary regimen will receive placebo at 6 months and 12 months after completion of the primary regimen[a] (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.

[a] At the time of unblinding, after EUA or approval in any country and local approval of Protocol Amendment 10, only the Group 5 (placebo only) participants not willing to receive a single dose of 5×10^{10} vp Ad26.COV2.S or another authorized/licensed COVID-19 vaccine will continue Group 5 booster vaccinations in Cohort 2 (refer to Section 8.6).

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 [e] N/A per Amendment 16
1 [d]	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 [d]	30	Ad26.COV2.S 5×10^{10} vp	Placebo	Placebo	Ad26.COV2.S 5×10^{10} vp
5 [c]	15	Placebo	Placebo [c]	Placebo [c]	Placebo [c]
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 and 12 months after completion of the single-dose primary regimen.
c. At the time of unblinding, after EUA or approval in any country and local approval of Protocol Amendment 10, only the Group 5 (placebo only) participants not willing to receive a single dose of 5×10^{10} vp Ad26.COV2.S or another authorized/licensed COVID-19 vaccine will continue Group 5 booster vaccinations in Cohort 2a (refer to Section 8.6).
d. Applicable to the US only; Following local approval of Protocol Amendment 15, all participants of Groups 1 and 4 not willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will continue booster vaccinations in Cohort 2a according to their current schedule.
e. Following local approval of Protocol Amendment 16, booster vaccinations (either placebo or Ad26.COV2.S $5x10^{10}$ vp) will not be administered at 24 months after completion of the primary regimen.

EUA = Emergency Use Authorization; N = number of participants; N/A = not applicable; 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 [e] N/A per Amendment 16
1 [d]	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 [d]	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 [c]	15	Placebo	Placebo	Placebo [c]	Placebo [c]	Placebo [c]
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 and 12 months after completion of the 2-dose primary regimen. If the 2nd vaccination at Day 57 is not provided, then participants will discontinue the study (refer to Section 7.2).
c. At the time of unblinding, after EUA or approval in any country and local approval of Protocol Amendment 10, only the Group 5 (placebo only) participants not willing to receive a single dose of 5×10^{10} vp Ad26.COV2.S or

another authorized/licensed COVID-19 vaccine will continue Group 5 booster vaccinations in Cohort 2b (refer to Section 8.6).

d. Applicable to the US only: Following local approval of Protocol Amendment 15, all participants of Groups 1 and 4 not willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will continue booster vaccinations in Cohort 2b according to their current schedule.

e. Following local approval of Protocol Amendment 16, booster vaccinations (either placebo or Ad26.COV2.S $5x10^{10}$ vp) will not be administered at 26 months after completion of the primary regimen.

EUA = Emergency Use Authorization; N = number of participants; N/A = not applicable; 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 participants, 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). In case participants consent for the additional follow-up (see SoA in Section 1.3.9), the study duration from screening until the last follow-up visit will be approximately 27 months per participant. For these participants, 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 24 months after the second vaccination (Target Visit Day 787±21 days).

For Cohort 2a, the study duration from screening until the last follow-up visit will be approximately 24 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 or 12 months after completion of the single-dose primary regimen on Day 1 and follow-up visits up to 24 months after completion of the primary regimen on Day 1 (Target Visit Day 731±21 days).

For Cohort 2b, the study duration from screening until the last follow-up visit will be approximately 24 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 or 12 months after completion of the 2-dose primary regimen on Day 57, and follow-up visits up to 24 months after completion of the primary regimen on Day 57 (Target Visit Day 787±21 days). If the 2nd vaccination at Day 57 is not provided, then participants will discontinue the study (refer to Section 7.2).

Group 5 (placebo only) participants who wish to receive a single dose of 5×10^{10} vp Ad26.COV2.S (ie, at the time of unblinding, after EUA or approval in any country and local approval of protocol Amendment 10), will discontinue from participation in the placebo groups (refer to Sections 7.4 and 8.6). This will reduce study duration for all Cohort 2 and for some of the Cohort 1 and 3 participants. For Cohorts 1a, 1b, and 3, the safety follow-up will end at Day 422 (ie, the initially planned study completion date) or 6 months after vaccination, whichever comes first. For Cohorts 2a and 2b, the safety follow-up will end 6 months after vaccination.

All eligible participants who wish to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S (ie, at the time of local approval of protocol Amendment 15), will discontinue from participation in their current schedules (refer to Sections 7.5 and 8.7). In this case, the safety and immunogenicity follow-up will end 6 months after the ad hoc booster vaccination.

For each cohort, if a participant is unable to complete the study, but has not withdrawn consent, is not lost to follow-up, or has not died, 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, SAEs, and AESIs. 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 15 minutes to 1 hour depending on the vaccination being administered (see SoAs for details) 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. Following local approval of protocol Amendment 15, participants will not be required to complete the booklet but will be contacted by the site regularly to check whether they experienced COVID-19 like symptoms. See Section 8.1.2.3 for the prespecified criteria for suspected COVID-19. Prior to the local approval of Protocol Amendment 16, 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 or until sign and symptom resolution, whichever comes first. Long-term sequelae of COVID-19 (eg, anosmia, headache, fatigue, and other symptoms at the investigator's judgement) will not be followed until their resolution if not resolved within a month.
- 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 sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

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

As of local approval of Protocol Amendment 16, participants will continue to be required to report safety events, such as SAEs, AEs, and AESIs. The active follow-up of new suspected COVID-19 episodes will be replaced by passive follow-up at scheduled study visits to document COVID-19 events as SAEs or AEs, if applicable (See Section 1.3.6.1).

For enrolled participants who received placebo only during primary regimen and who are accepting a single dose of 5×10^{10} vp Ad26.COV2.S offered at the time of unblinding, after EUA or approval in any country and local approval of protocol Amendment 10, procedures outlined in Section 8.6 apply. A single dose of 5×10^{10} vp Ad26.COV2.S will be administered during an ad hoc crossover visit and participants will remain under observation at the study site for at least 15 minutes following vaccination. SAEs, special reporting situations (whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products), and COVID-19-like signs and symptoms will be reported from the time of unblinding until the end-of-safety-follow-up phone call. In addition, suspected AESIs will be reported from the time of vaccination until the end-of-safety-follow-up phone call after local approval of protocol Amendment 11 is obtained.

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.

Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is locally approved by the Health Authority and IEC/IRB, will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo only will be offered a single dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in the placebo groups (refer to Section 7.4). For more details regarding procedures after EUA, refer to Section 8.6. Statistical analysis of data obtained from the point of unblinding is outlined in Section 9.7.

Biomarker Collection

For all participants, biomarker analysis (PAXgene, RNA-seq) will be performed to explore potentially informative biomarkers related to vaccine immunogenicity and SARS-CoV-2 infection (including relations with COVID-19 disease severity). 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,[47,48] 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.[7]

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. In case participants consent for the additional follow-up (see SoA in Section 1.3.9), they will be considered to have completed the study if he or she has completed assessments at Day 787. Participants who prematurely discontinue study vaccine for any reason before completion of the last study visit 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.

Group 5 (placebo only) participants who wish to receive a single dose of 5×10^{10} vp Ad26.COV2.S (ie, at the time of unblinding, after EUA or approval in any country and approval of protocol Amendment 10), will discontinue from participation in the placebo groups (refer to Sections 7.4 and 8.6). This will reduce study duration for all Cohort 2 and for some of the Cohort 1 and 3 participants. For Cohorts 1a, 1b, and 3, the safety follow-up will end at Day 422 (ie, the initially planned study completion date) or 6 months after vaccination, whichever comes first. For Cohorts 2a and 2b, the safety follow-up will end 6 months after vaccination. At that time, the participant will be contacted (phone call) by the site with regards to SAE and AESI collection, after which the participant will be considered to have completed the study.

All eligible participants who wish to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S (ie, at the time of local approval of protocol Amendment 15), will discontinue from participation in their current schedules (refer to Sections 7.5 and 8.7). In this case, the safety and immunogenicity follow-up will end 6 months after the ad hoc booster vaccination.

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.

Following local approval of protocol Amendment 10, after unblinding, participants who initially received placebo only are offered to receive a single dose of 5×10^{10} vp Ad26.COV2.S at the study site (ie, placebo crossover vaccination). Eligibility criteria to receive the placebo crossover vaccination are described in Section 8.6.

Following local approval of protocol Amendment 15, a single ad hoc booster vaccination with Ad26.COV2.S at the $5x10^{10}$ vp dose level will be offered to all eligible participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an

mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Eligibility criteria to receive the ad hoc booster vaccination are described in Section 8.7.

The following ongoing participants will not be eligible to receive this ad hoc booster vaccination:

Group 5 participants (all cohorts) who crossed over from placebo to receive Ad26.COV2.S at the $5x10^{10}$ vp dose level (ie, placebo crossover vaccination) (see Section 1.3.7).

Group 5 participants (all cohorts) who did not opt for the placebo crossover vaccination and therefore have not received any vaccination with the Ad26.COV2.S vaccine.

Cohort 2 participants who will receive a booster vaccination according to their initial schedule at 6 and 12 months after the primary regimen (Groups 2 and 3, respectively) (see Section 4.1).

Applicable to Belgium only: Per the Belgian-specific protocol Amendment 15, participants aged <65 years enrolled at Belgian sites.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria[a] 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:

[a] See also criteria for participants receiving a single ad hoc booster dose of $5x10^{10}$ vp Ad26.COV2.S described in Section 8.7.

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-19.11

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].11 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);

[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.

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.*

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 Criterion modified per Amendment 8:

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

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

   c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of study vaccine and during the study.

5. Criterion modified per Amendment 3:

   5.1 Participant has a history of any neurological disorders or seizures including Guillain-Barré syndrome (GBS), 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 Criterion modified per Amendment 7:

   9.2 Criterion modified per Amendment 8:

   9.3 Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational Ig or monoclonal antibodies within 3 months, or

received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the 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.

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

The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination (see also Exclusion Criterion 20) and during the study except under the conditions described in Section 6.6.

10. Criterion modified per Amendment 15:

    10.1 Criterion modified as per Amendment 16:

    10.2 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. Note (Applicable to the US only): Following local approval of Protocol Amendment 15, participants who are pregnant may receive ad hoc booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus (see Section 8.7).

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 Criterion modified per Amendment 8:

    22.2 Based on a serological test for SARS-CoV-2-specific antibodies 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:

    23.5 Criterion modified per Amendment 8:

    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 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and (pulmonary) hypertension or high blood pressure; obesity (BMI ≥30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic

[a]Per US CDC (See Section 10.10, Appendix 10). Gestational diabetes was deleted from the list since it is not applicable as pregnant women are not allowed to participate in the study.

conditions (dementia); smoking; end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; and sleep apnea.

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 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.

At the time of unblinding (ie, after EUA or approval in any country and local protocol Amendment 10 approval), a single dose of 5×10^{10} vp Ad26.COV2.S will be offered to Group 5 (placebo only) participants during an ad hoc crossover visit (refer to Section 8.6). If any of the above listed events occur at the time of the planned ad hoc visit, the visit can be postponed till symptoms have resolved.

Following local approval of protocol Amendment 15, all eligible participants (see Section 8.7) will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19

vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. If any of the above listed events occur at the scheduled time for the ad hoc booster vaccination, the booster vaccination visit with active vaccine can be delayed within the preferred visit window (see Section 8.7).

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 and dosed at $5x10^{10}$ vp and $1x10^{11}$ vp. 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.

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

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

For participants who received placebo only during primary regimen and who are offered a single dose of $5×10^{10}$ vp Ad26.COV2.S at the time of unblinding (ie, after EUA or approval in any country and local Amendment 10 approval), a dose level of $5×10^{10}$ vp in a volume of 0.5 mL will be administered.

Following local approval of protocol Amendment 15, for all eligible participants who are offered a single ad hoc booster dose of $5×10^{10}$ vp Ad26.COV2.S, a dose level of $5×10^{10}$ vp in a volume of 0.5 mL will be administered.

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. In addition, if IWRS cannot be updated to allow dispensing of investigational product to Cohort 2 participants who have previously been unblinded but did not receive and authorized/licensed COVID-19 vaccine, manual assignment of kits may be performed.

Blinding Before EUA or Approval in any Country and Local Protocol Amendment 10 Approval

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.

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.

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

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no clinical data on the safety of receiving a different COVID-19 vaccine after receiving Ad26.COV2.S.

In the event of a participant unblinding to receive an authorized/licensed COVID-19 vaccine and the participant received an authorized/licensed COVID-19 vaccine outside of the study, no further

study vaccination will be permitted[a]. Unblinded participants, that did not receive an authorized/licensed COVID-19 vaccine outside of the study, will be asked to continue to be followed in this study in line with the SoA to the extent that they permit, including Cohort 2 booster vaccinations.

Safety and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. Procedures installed at the time of unblinding all participants after EUA or approval in any country and local approval of protocol Amendment 10 (refer to Section 8.6), will also apply to participants who were unblinded at their own request prior to Amendment 10. For details regarding statistical analysis of these evaluations, refer to Sections 9.6 and 9.7.

Unblinding after EUA or Approval in any Country and Local Protocol Amendment 10 Approval

Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is approved locally by the Health Authority and IEC/IRB will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo only will be offered a single dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in the placebo groups. Refer to Sections 7.4 and 8.6 for more details.

Statistical analysis of data obtained from the point of unblinding is outlined in Section 9.7.

Unblinding after Protocol Amendment 15 Approval (Ad Hoc Booster Vaccination)

Following local approval of Amendment 15 by the Health Authority and IEC/IRB, participants in Group 1 and 4 of Cohort 2 will be partially unblinded. After unblinding, enrolled eligible participants from Groups 1 and 4 of Cohort 2 will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in their current booster schedule. Refer to Sections 7.5 and 8.7 for more details.

Statistical analysis of data obtained from the point of unblinding is outlined in Section 9.8.

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.

[a] Following local approval of protocol Amendment 15, eligible participants who received an authorized/licensed COVID-19 vaccine outside of the study are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.

6.5. Dose Modification

Dose modification is not applicable in this study.

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

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

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

At the time when a COVID-19 vaccine is determined to be efficacious and authorized/licensed for use, some participants may become eligible to receive such vaccine, depending on country-specific conditions (eg, registration status, local recommendations/regulations, vaccine availability or the specific target group for vaccination). The investigator will discuss with the participants the available information and options to allow the participant to make an informed choice as to whether they qualify to receive the authorized/licensed vaccine and whether they should request individual unblinding to take up the offer of an authorized/licensed COVID-19 vaccine. In the event of a participant unblinding to receive an authorized/licensed COVID-19 vaccine, and the participant received an authorized/licensed COVID-19 vaccine outside of the study, no further study vaccination will be permitted[a]. Unblinded participants, whether in the vaccine or control group that did not did not receive an authorized/licensed COVID-19 vaccine outside of the study, will be asked to continue to be followed in this study in line with the schedule of activities to the extent that they permit, including Cohort 2 booster vaccinations. Safety and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. All data will be analyzed separately from the point of unblinding under the conditions outlined in Sections 6.3 and 9.6.

Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is locally approved by the Health Authority and IEC/IRB will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo

[a] Following local approval of protocol Amendment 15, eligible participants who received an authorized/licensed COVID-19 vaccine outside of the study are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.

only will be offered a single dose of 5×10^{10} vp Ad26.COV2.S. If willing to receive, they will discontinue from participation in the placebo groups. Refer to Sections 7.4 and 8.6 for more details.

Following local approval of protocol Amendment 15, all eligible participants will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S at no cost, as described in Section 8.7. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Analyses and procedures installed at the time of unblinding all participants after EUA or approval in any country and local approval of protocol Amendment 10 (refer to Section 8.6), will also apply to participants who were unblinded at their own request prior to Amendment 10.

6.7. Treatment of Overdose

For this study, any dose of Ad26.COV2.S greater than the highest dose tested in the study 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 15 minutes or 1 hour depending on the vaccination being administered (see SoAs for details) 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.

Concomitant therapies associated with a suspected AESI meeting the criteria outlined in Section 8.3.6, will be recorded.

Receipt of a licensed/authorized COVID-19 vaccine by a study participant at any timepoint during the study must be recorded. The name and date(s) of administration of the COVID-19 vaccine should be recorded. 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. Participants from Cohorts 1a, 1b and 3, who received additional/booster COVID-19 vaccines outside of the study during the additional follow-up of the study, should be allowed to stay in the study, however these vaccines should be recorded in the Concomitant Medications section of the eCRF.

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 received a COVID-19 vaccine outside of the study, or treatment, will not receive further study vaccination[a]. Participants may not receive an investigational drug (including investigational drugs for prophylaxis of COVID-19) or use an invasive investigational medical device within 30 days or receive investigational Ig or monoclonal antibodies within 3 months, or receive convalescent serum for COVID-19 treatment within 4 months or receive an investigational vaccine (including investigational Adenoviral-vectored vaccines) 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 or recurrent use of systemic corticosteroids[b] at immunosuppressive dose, 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.

[a] Following local approval of protocol Amendment 15, eligible participants who received an authorized/licensed COVID-19 vaccine outside of the study are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.

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

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

Upon completion of all Day 57 vaccinations in all cohorts, the study pausing criteria as outlined below are no longer applicable.

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

   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].
7. A study pause is triggered in Studies VAC31518COV1002, VAC31518COV2001, or VAC31518COV3001.

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.

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 paused by the DRC 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. The decision from the DRC will be forwarded by the

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

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
    - Note: Applicable to the US only: Following local approval of Protocol Amendment 15, participants who are pregnant may receive booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus (see Section 8.7).
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- The participant received an authorized/licensed COVID-19 vaccine outside of the study.
    - Note: following local approval of protocol Amendment 15, eligible participants (see Section 8.7) are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic or recurrent use of systemic corticosteroids and administration of antineoplastic and immunomodulating agents or radiotherapy
- Withdrawal from further study vaccination
- Participant has a positive test result for SARS-CoV-2 infection during the study (see Section 8.1.2). Note: participants may receive a placebo crossover vaccination or ad hoc booster vaccination with the Ad26.COV2.S vaccine after they have recovered from the acute illness and at least 3 months have passed as specified in Sections 8.6 and 8.7.
- Participant receives any experimental medication (including experimental vaccines other than the study vaccine) or receives a COVID-19 treatment
- Participant previously experienced TTS, or heparin-induced thrombocytopenia (HIT) or GBS.

- Participant experiences capillary leak syndrome (CLS) after the first dose.
- Applicable to Belgium only: Per the Belgian-specific protocol Amendment 15, participants aged <65 years enrolled at Belgian sites.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent from the study
- Death
- Repeated failure to comply with protocol requirements
- Participant in Cohort 2b does not have the second study vaccination on Day 57 (-3/+7 days), except for when the vaccination was missed due to a confirmed SARS-CoV-2 infection (refer to Sections 7.1 and 8.1.2)
- Participants who received placebo only during primary regimen and who cho(o)se to receive an authorized/licensed vaccine outside of the study (applies to participants unblinded before and after EUA or approval in any country), once protocol Amendment 10 has been implemented locally

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, lost to follow-up, or death, then no additional assessments are required, but an optional safety visit will still be offered.

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.

7.4. Discontinue from Placebo Group Participation

Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is locally approved by the Health Authority and IEC/IRB will be unblinded to disclose who received placebo only during primary regimen. After unblinding, enrolled participants who initially received placebo only will be offered a single dose of 5×10^{10} vp Ad26.COV2.S (ie, placebo crossover vaccination). If willing to receive, they will discontinue from participation in the placebo groups. They will be redirected to SoA "Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S (Placebo Crossover Vaccination) after EUA or Approval in any Country" (see Section 1.3.7). Refer to Section 8.6 for more details regarding assessments and procedures after EUA approval.

7.5. Discontinue from Cohort Vaccination

Following local approval of protocol Amendment 15, all eligible participants (see Section 8.7) will be offered a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp). The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. If willing to receive, they will discontinue from participation in their current schedules (SoAs in Sections 1.3.1, 1.3.2, 1.3.3.2, 1.3.4.2, 1.3.5, and 1.3.9) and will be redirected to SoA "Procedures for Participants Receiving an Ad Hoc Booster Vaccination of $5x10^{10}$ vp Ad26.COV2.S" (see Section 1.3.10).

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 8.1.2.3, 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 965 mL for Cohorts 1a or 3, 1,225 mL for Cohort 1b, 514.5 mL for Cohort 2a and 752.5 mL for Cohort 2b. For participants who undergo additional procedures due to COVID-19-like signs and symptoms, an additional approximately 17.5 mL of blood will be collected. For participants who experience a suspected AESI, an additional approximately 30 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.

For participants who receive an ad hoc booster vaccination of $5x10^{10}$ vp Ad26.COV2.S, up to a maximum of 284 mL of blood will be collected additionally.

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 scheduled using the date that the vaccination was scheduled to take place.

If a vaccination window is missed due to a study pause (see Section 6.9), efforts will be made to still vaccinate the participant as soon as possible. Visit windows for vaccination visits will not apply for study pauses or vaccination pauses. The timings of the post vaccination visits will be determined relative to the actual day of the vaccination, unless they overlap with other scheduled visits, in which case the sponsor should be contacted to discuss optimal scheduling for these visits.

Table 4: Visit Windows Cohort 1a

Visit[c]	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
FU1	513[b]	±21 days	15 months post-vaccination 2 safety telephone call (visit if necessary)
FU2	604[b]	±21 days	18 months post-vaccination 2 safety and immunogenicity visit
FU3	696[b]	±21 days	21 months post-vaccination 2 safety telephone call (visit if necessary)
FU4	787[b]	±21 days	24 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.

c. Following local approval of Protocol Amendment 15, all eligible participants willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will discontinue their cohort schedule and follow the procedures in Table 9.

Table 5: Visit Windows Cohort 1b

Visit[e]	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
13a[b, c]	422[d]	-21/+60 days	LNA safety and immunogenicity visit
13b[b, c]	425	±1 day	72 hours post-LNA safety follow-up telephone call
13c[b, c]	429	±1 day	1 week post-LNA safety visit
FU1	513[b]	±21 days	15 months post-vaccination 2 safety telephone call (visit if necessary)
FU2	604[b]	±21 days	18 months post-vaccination 2 safety and immunogenicity visit
FU3	696[b]	±21 days	21 months post-vaccination 2 safety telephone call (visit if necessary)
FU4	787[b]	±21 days	24 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.

c. Visit 13a, 13b, and 13c are visits for Cohort 1b participants that provided consent for the optional LNAs.

d. The LNA may occur at Day 422 (in this case Visit 13 and optional Visit 13a will coincide) or will be performed at a later timepoint within the specified window (Day 422 -21/+60).

e. Following local approval of Protocol Amendment 15, all eligible participants willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will discontinue their cohort schedule and follow the procedures in Table 9.

Table 6: Visit Windows Cohort 2a

Visit[d]	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 [e]	731	±21 days	Safety

a. If a participant comes in early for Visit 3, 6, 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. 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 or 12 months after completion of the single-dose primary regimen and will receive placebo at the other indicated time point. Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 2 for further details.

d. Following local approval of Protocol Amendment 15, all eligible participants of Groups 1 and 4 willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will discontinue their cohort schedule and follow the procedures in Table 9

e. Visit 11 is the last visit.

Table 7: Visit Windows Cohort 2b

Visit [c]	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 [e]	787 [b]	±21 days	Safety

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 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 or 12 months after completion of the 2-dose primary regimen and will receive placebo at the other indicated time point. If the 2nd vaccination at Day 57 is not provided, then participants will discontinue the study (refer to Section 7.2). Participants not designated to receive a booster vaccination will receive placebo at each indicated time point. See Table 3 for further details.

d. Following local approval of Protocol Amendment 15, all eligible participants of Groups 1 and 4 willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will discontinue their cohort schedule and follow the procedures in Table 9.

e. Visit 14 is the last visit.

Table 8: Visit Windows Cohort 3

Visit[c]	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
FU1	513[b]	±21 days	15 months post-vaccination 2 safety visit
FU2	604[b]	±21 days	18 months post-vaccination 2 safety and immunogenicity visit
FU3	696[b]	±21 days	21 months post-vaccination 2 safety visit
FU4	787[b]	±21 days	24 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.

c. Following local approval of Protocol Amendment 15, all eligible participants willing to receive a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S will discontinue their cohort schedule and follow the procedures in Table 9.

Table 9: Visit Windows Ad Hoc Booster Vaccination

Visit	Target Visit Day	Allowed Window	Primary Purpose
Ad hoc booster visit (AHBV)	≥6 mo after last COVID-19 vaccination [a]	As soon as possible, but no later than 120 days post local approval of protocol amendment 15	Ad hoc booster vaccination
Booster FU1	AHBV + 28 days [b]	±3 days	Safety and immunogenicity visit 28 days post-booster vaccination
Booster FU2 [c]	AHBV + 182 days [b]	±21 days	Safety and immunogenicity visit 6 months post-booster vaccination

a. Following local approval of protocol amendment 15, a single ad hoc booster vaccination with Ad26.COV2.S at the $5x10^{10}$ vp dose level will be offered to all eligible participants. The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago.

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

c. Changes following local approval of Protocol Amendment 16 for participants who are attending ad hoc booster visit are provided in the Schedule of activities in Section 1.3.10.

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[a]. Participants who test positive for SARS-CoV-2 infection will be informed of the result by the study staff. 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

[a] Vaccination with Ad26.COV2.S may interfere with some serologic assays utilized at local community health clinics/commercial laboratories, by seeking and identifying the spike protein in the vaccine and rendering a false positive result. For this reason, participants will be encouraged to not seek serologic testing outside the study. If a participant requests serologic testing outside of the protocol-mandated testing schedule, this will be offered at the next scheduled on-site blood draw visit.

- 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), for participants with a positive test result for SARS-CoV-2 infection (Section 1.3.6), for additional follow-up for Cohorts 1a, 1b and 3 (Section 1.3.9), and for participants receiving an ad hoc booster vaccination (Section 1.3.10).

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 10 and Table 11 respectively.

Exploratory assessments on lymph node samples for Cohort 1b (Beth Israel Deaconess Medical Center [BIDMC]) may include, but are not limited to characterization of resident immune cells by flow cytometry, gene expression, and cytokine release (see Section 8.1.1.1).

Assays used for the double-blind phase and post unblinding of the study:

Table 10: 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 binding antibodies to S protein (MSD)	Analysis of antibodies binding to SARS-CoV-2 S protein and the RBD of SARS-CoV-2 S protein
SARS-CoV-2 neutralization (neutralization assay)	Analysis of neutralizing antibodies to the vaccine strain (or other lineage), 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; MSD = Meso Scale Discovery; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay

Table 11: 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)
Evaluation of germinal centers in lymph nodes (see Section 8.1.1.1)	Analysis of the immune responses in lymph nodes

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

Assays used for the ad hoc booster vaccination:

Table 12: Summary of Humoral Immunogenicity Assays

Assay	Purpose
Exploratory endpoints	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein from the original strain and/or emerging variants
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S and RBD protein from the original strain and/or emerging variants
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein
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
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; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay

Table 13: Summary of Cellular Immunogenicity Assays

Assay	Purpose
Exploratory 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

ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; TNFα = tumor necrosis factor alpha

8.1.1.1. Optional Lymph Node Aspiration

Late increases in neutralizing antibody responses to COVID-19 variants have been observed, suggesting ongoing B cell maturation. In this regard, there is an interest to study the immune responses in lymph nodes to better understand the increase in neutralizing activities of the antibodies against variants, generated by Ad26.COV2.S.

Fine-needle aspirates will be collected for Cohort 1b (Beth Israel Deaconess Medical Center [BIDMC]), preferably from the axillary lymph nodes draining the injection site (left or right deltoid), corresponding to the side where the participant received the vaccination, in those participants who consent to this optional procedure. For study participants who received open-label ad hoc Ad26.COV2.S vaccination, the side of that vaccination should be preferably used. A possible correlation between T-follicular helper cells, B-cell activation/specificity and the quality of antibody response will be evaluated (eg, by flow cytometry). Fine needle aspiration is a minimally invasive procedure routinely used by interventional radiologists and in cytopathology laboratories to access lymphoid tissues for clinical evaluation of various malignancies, infections and autoimmune diseases. Interventional radiologists are chosen to perform this procedure as ultrasound-guidance will be necessary to locate non-palpable lymph nodes; these are the type of lymph nodes most often encountered in healthy participants. If the interventional radiologist determines that obtaining an axillary sample would pose an increased risk to the participants, or it may be difficult to obtain adequate cell yield, sampling from axillary lymph nodes on the opposite body side, or cervical/inguinal lymph nodes may be considered. Prior to the LNA an anesthetic will be injected into the site of the procedure. At most, serial sampling of 1-2 lymph nodes will be performed (each lymph node will be sampled 4 times). If sampling of the first lymph node is very small, then there may be a need to sample a second lymph node.

The procedure will be performed at approximately 12 months after the 2^{nd} vaccination (active or placebo) or approximately 6 months after the ad hoc vaccination (for participants who crossed over from placebo to receive active Ad26.COV2.S $5x10^{10}$ vp vaccination) in Cohort 1b participants that have provided consent.

A study coordinator or study clinician will contact the participant by phone within 72 hours after the procedure to further follow-up on the safety. Study staff will coordinate if the participant prefers to schedule an in person visit for the follow-up contact. The participant will be asked questions regarding any ongoing bleeding, pain control, and signs or symptoms of infection. Participants contacted by a study coordinator will be asked if they would like to speak with a study clinician to review their health status. Findings need to be collected as AEs related to the optional

LNA procedure. In addition, AEs related to the optional LNA procedure will be collected 1 week after the LNA.

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

8.1.2.1. Passive Follow-up (As of Local Approval of Protocol Amendment 16)

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 1.3.6.1.

As of Amendment 16, active follow-up of suspected COVID-19 episodes will be replaced by a passive follow-up approach. For COVID-19 events that are ongoing at the time of local approval of Protocol Amendment 16:

a. Participant will no longer complete the SIC.

b. Any outstanding activities planned for the follow-up of COVID-19 events will end.

c. No further sampling for participants and no Day 1-4, Day 3-8, and Day 29 visit will be performed.

For new suspected COVID-19 episodes no samples will be collected in the context of the study. Site staff will collect information on new COVID-19 episodes at scheduled visits and report these as SAEs or AEs, as applicable. Participants may also contact the site at any time in between scheduled visits to report a safety concern (eg, hospitalization) or COVID-19 episodes. Concomitant medications for each COVID-19 episode are to be reported into the eCRF as well as any laboratory confirmation of COVID-19, if available.

8.1.2.2. Active Follow-up (Prior to Local Approval of Protocol Amendment 16)

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 1.3.6.2.

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms. Following local approval of protocol Amendment 15, participants will not be required to complete the booklet but will be contacted by the site regularly to check whether they experienced COVID-19 like symptoms. See Section 8.1.2.3 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 or until sign and symptom resolution, whichever comes first. Long-term sequelae of COVID-19 (eg, anosmia, headache, fatigue, and other symptoms at the investigator's judgement) will not be followed until their resolution if not resolved within a month.
- 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 (see section 7.1), unless they withdraw consent from the study (see section 7.2). The participant will be followed until resolution of clinical symptoms (except for long-term sequelae of COVID-19).

The sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

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

8.1.2.3. 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

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

8.1.3. Procedures in Case of Asymptomatic COVID-19 RT-PCR Confirmed Infection

Passive Follow-up (As of local approval of Protocol Amendment 16)

- Participants will report any positive RT-PCR SARS-CoV-2 test results during their scheduled visit.

Active Follow-up (Prior to local approval of Protocol Amendment 16)

For each cohort, if participants receive a positive RT-PCR SARS-CoV-2 result from a private/off-study test, without experiencing any COVID-19 symptoms, the following should take place:

- Participants should contact the study site at the time the positive RT-PCR SARS-CoV-2 test result is obtained.
- The study staff should ensure the participant's medical care provider has been/will be informed. The sponsor recommends to contact the participant at least once per week, and recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

The above must be done in accordance with local country and site level recommendations for COVID-19, and these participants will not be permitted to receive further study vaccination administrations (see Section 7.1). The participant can continue in the study for safety and immunogenicity assessments, unless they withdraw consent from the study (see Section 7.2).

In the event a participant experiences COVID-19-like signs or symptoms after obtaining a positive RT-PCR SARS-CoV-2 test result, procedures as described in Section 8.1.2 should be followed

with the exception of nasal swab collection to assess the presence of SARS-CoV-2 infection or influenza infection.

8.1.4. 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-, 18- and 24-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 (SoA).

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. This symptom-directed physical examination will also include basic neurological examination, if

warranted. 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 clinical laboratory assessments (as detailed in Section 10.2, Appendix 2) will be collected as described in the Schedules of Activities in Section 1.3. In case of a suspected AESI, every effort should be made to collect local hospital/laboratory test results obtained by the treating physician to allow rapid diagnosis and treatment. This information should be reported through the TTS AESI form (see Section 10.11, Appendix 11) electronically per instructions in the eCRF completion guidelines. In addition, every effort should be made to collect blood samples from the participant for a platelet count (local laboratory or substitute for local laboratory) and other applicable testing (central laboratory) (see the Schedule of Activities in Section 1.3 and Section 10.2, Appendix 2). The Investigator will review the laboratory test results to assist the investigation of the AESI.

See Section 8.3.6 for details on laboratory test details to be reported for an AE of thrombocytopenia.

8.3. Adverse Events, Adverse Events of Special Interest, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, suspected AESIs, 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, suspected AESIs, 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.

For enrolled participants who received placebo only during primary regimen and who are accepting a single dose of 5×10^{10} vp Ad26.COV2.S offered at the time of unblinding, after EUA or approval in any country and local approval of protocol Amendment 10, procedures outlined in Section 8.6 apply. A single dose of 5×10^{10} vp Ad26.COV2.S will be administered during an ad crossover hoc visit and participants will remain under observation at the study site for at least 15 minutes following vaccination. SAEs, special reporting situations (whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products), and COVID-19-like signs and symptoms will be reported from the time of unblinding until the end-of-safety-follow-up phone call. In addition, suspected AESIs will be reported after local approval of protocol Amendment 11 is obtained.

8.3.1. Time Period and Frequency for Collecting Adverse Event, Adverse Events of Special Interest, and Serious Adverse Event Information

All Adverse Events

For all cohorts, 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. Suspected AESIs will be reported once local approval of protocol Amendment 11 is obtained until the end of the study/early withdrawal.

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

As of protocol Amendment 16, for all participants:

- A passive follow-up approach is adopted, defined as on-site study visits to document new COVID-19 events as SAEs or AEs, as applicable. Participants may also contact the site at any time in between scheduled visits to report a safety concern (eg, hospitalization) or COVID-19 episodes.
- Concomitant medications for these events should be reported.
- If a COVID-19 confirmatory laboratory or assay read-out is available, this should be reported in the eCRF together with the method of the test if known.

Adverse Events of Special Interest

From the time of local approval of protocol Amendment 11 onwards, TTS is considered an AESI. Suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below 150,000/μL[9]]) will be reported until the end of the study/early withdrawal. An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS (see Section 8.3.6).

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, Adverse Events of Special Interest, and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs, suspected AESIs, 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 15 minutes to 1 hour depending on the vaccination being administered (see SoAs for details) 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.[28,36]

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.[41]

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.

For details about AESIs, refer to Section 8.3.6.

8.3.3. Follow-up of Adverse Events, Adverse Events of Special Interest, 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, AESI, 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.

Applicable to the US only: Following local approval of protocol Amendment 15, participants who are pregnant may receive ad hoc booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus (see Section 8.7).

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

8.3.6. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known or suspected class effects, or based on nonclinical signals. Adverse events of special interest will be carefully monitored during the study by the sponsor.

AESIs must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious AEs) or causality following the procedure described above for SAEs.

Specific requirements for the AESI are described below.

8.3.6.1. Thrombosis with Thrombocytopenia Syndrome

As described in Section 2.3.1, Risks Related to Study Participation, TTS has been observed very rarely following vaccination with Ad26.COV2.S and is considered to be an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia.[3,9]

Because this syndrome is rare and not completely understood, all cases of thrombosis and/or thrombocytopenia will be considered a suspected case of TTS until further adjudication can be performed. An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS. The investigator shall be responsible for reporting any suspected AESI of TTS using the SAE form and the form detailed in Section 10.11, Appendix 11. A suspected TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 10.12, Appendix 12
- Thrombocytopenia, defined as platelet count below 150,000/μL[9]

Symptoms, signs, or conditions suggestive of a thrombotic event should be recorded and reported as a suspected AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely. Follow-up information and final diagnoses, if applicable, should be submitted to the sponsor as soon as they become available.

In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used.

For either a thrombotic event or thrombocytopenia, testing for anti-PF4 should be performed at the local laboratory or substitute local laboratory; repeat testing may be requested for confirmation upon sponsor discretion.

Suspected AESIs will require enhanced data collection and evaluation (see Section 1.3.8). Every effort should be made to report as much information as possible about the AESI to the sponsor in a reasonable timeframe.

If an event meets the criteria for an SAE (Section 10.4.1), it should be reported using the same process as for other SAEs.

The form detailed in Section 10.11, Appendix 11 is intended as a guide for assessment of the AESIs to facilitate diagnosis and determine treatment options. If the investigator is not the treating physician, every effort should be made to collect the information requested in the form from the treating physician and enter the available information in the eCRF.

The sponsor will also attempt to collect information from any thrombotic event/thrombocytopenia/TTS reported prior to protocol Amendment 11.

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 all participants, biomarker analysis (PAXgene, RNA-seq) will be performed to explore potentially informative biomarkers related to vaccine immunogenicity and SARS-CoV-2 infection (including relations with COVID-19 disease severity). 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).

8.6. Assessments and Procedures after EUA or Approval in any Country

Following EUA, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is approved locally by the Health Authority and IEC/IRB, will be unblinded to disclose who received placebo only during primary regimen.

The Procedures detailed in this section also apply to participants who were unblinded at their own request prior to Amendment 10.

In general, after unblinding, participants who initially received placebo only, can elect to receive a single dose of 5×10^{10} vp Ad26.COV2.S offered at the study site (ie, placebo crossover vaccination), can opt to receive an authorized/licensed COVID-19 vaccine outside of the study, or may choose not to receive any additional vaccinations. Participants who received active vaccine will be asked to continue in the study or can opt to receive an authorized/licensed COVID-19 vaccine outside of the study.

All currently enrolled participants will be contacted by the study site to inform them whether they received active vaccine or placebo only. Participants will be counseled regarding the importance to continue practicing preventative measures to limit the spread of the disease including social

distancing, wearing face masks, and frequent hand washing, in compliance with local and national guidelines. This contact will be documented in the source documents.

Participants in the active vaccine groups will be informed they received at a minimum the dose level approved for Emergency Use (single-dose regimen of $5x10^{10}$ vp Ad26.COV2.S) and will be asked to continue to be followed in this study in line with the Schedule of Activities (SoA). For participants who were unblinded (at any time) and did not receive an authorized/licensed COVID-19 vaccine outside of the study, they will be permitted to receive the Cohort 2 booster vaccinations. If they opt to receive an authorized/licensed COVID-19 vaccine outside of the study, they will be discontinued from further study vaccination (see Section 7.1).

Participants who received placebo only during primary regimen, will be offered a single dose of 5×10^{10} vp Ad26.COV2.S (ie, placebo crossover vaccination). If willing to receive, they will discontinue from participation in the placebo groups (see Section 7.4). If they opt to receive an authorized/licensed COVID-19 vaccine outside of the study, they will discontinue the study (see Section 7.2). If they choose not to receive an authorized/licensed COVID-19 vaccine outside of the study, they will be asked to continue to be followed in this study in line with the Schedule of Activities (SoA), including Cohort 2 booster vaccinations.

Criteria for Group 5 (Placebo Only) Participants to Receive a Single Dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or Approval in any Country

- Participants have to be actively enrolled in the study.
- Participants have not received an authorized/licensed COVID-19 vaccine outside of the study.
- Participants, who were already unblinded for any reason, might receive a single dose of $5x10^{10}$ vp Ad26.COV2.S vaccine at the investigator's discretion, provided they did not receive another licensed/authorized COVID-19 vaccine.
- Participants who have become infected with SARS-CoV-2 during the double-blind phase of the study may receive a single dose of $5x10^{10}$ vp Ad26.COV2.S vaccine after being made aware that the safety and efficacy data on vaccinating a previously infected individual is limited.
- Participants should not have previously experienced TTS, HIT, or GBS.
- Participant should not have previously experienced CLS

Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or Approval in any Country

Participants who received placebo only during primary regimen accepting a single dose of 5×10^{10} vp Ad26.COV2.S, will discontinue from participation in the placebo groups (see Section 7.4). They will be redirected to SoA 'Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S (Placebo Crossover Vaccination) after EUA or Approval in any Country' (see Section 1.3.7).

Vaccination will be planned during an ad hoc crossover visit as soon as the site is operationally ready. A urine pregnancy test will be collected from all women of childbearing potential (Cohorts 1 and 2) and a blood sample for a platelet count (as part of a complete blood count if applicable) will be collected from all participants prior to vaccination. Vaccination will be performed by a trained and qualified study nurse, medical doctor, or otherwise qualified HCP. Participants will remain under observation at the study site for at least 15 minutes for the presence of any acute reactions. SAEs, special reporting situations (whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products), and COVID-19-like signs and symptoms (refer to Section 8.1.2) will be reported from the time of unblinding until the end of safety follow-up/early withdrawal. In addition, AESIs will be reported after local approval of protocol Amendment 11 is obtained until the end of safety follow-up/early withdrawal. For Cohorts 1a, 1b, and 3, the safety follow-up will end at Day 422 (ie, the initially planned study completion date) or 6 months after vaccination, whichever comes first. For Cohorts 2a and 2b, the safety follow-up will end 6 months after vaccination. At that time, the participant will be contacted (phone call) by the site with regards to AESI and SAE collection, after which the participant will be considered to have completed the study.

8.7. Assessments and Procedures after Protocol Amendment 15 Approval (Ad Hoc Booster Vaccination)

Ad Hoc Booster Vaccination

Following local approval of protocol Amendment 15, all eligible participants will be offered a single ad hoc booster dose of 5×10^{10} vp Ad26.COV2.S.

As soon as possible, but no later than 120 days post local approval of protocol amendment 15, the ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID-19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Participants are free to choose to delay the booster vaccination within the window of the booster vaccination visit, to receive booster vaccination outside the study, or not to receive booster vaccination. Participants who choose to receive an outside of the study booster vaccination with the Ad26.COV2.S vaccine (if recommended by local authorities and available) or another authorized COVID-19 vaccine, choose not to receive an ad hoc booster vaccination, or are not eligible to receive the ad hoc booster vaccination, will not be withdrawn from the study and will be encouraged to remain in the study.

Participants in Group 1 and 4 of Cohort 2 will be partially unblinded. See Section 6.3 for more details.

Participants will be counseled regarding the importance to continue practicing preventative measures to limit the spread of the disease including social distancing, wearing face masks, and frequent hand washing, in compliance with local and national guidelines. This contact will be documented in the source documents.

Criteria for Participants Receiving a Single Ad Hoc Booster Dose of $5x10^{10}$ vp Ad26.COV2.S:

- Participants have to be actively enrolled in the study.
- Participants have not received any COVID-19-related experimental medication (including any experimental vaccine other than the study vaccine).
- Participants who have become infected with SARS-CoV-2 during the study may receive booster vaccination with the Ad26.COV2.S vaccine after they have recovered from the acute illness and at least 3 months have passed. Such participants should be made aware that the safety and efficacy data on vaccinating a previously infected individual is limited.
- Participants should not have previously experienced TTS, HIT, or GBS.
- Participant should not have previously experienced CLS.
- Applicable to the US only: Participants who are pregnant may receive ad hoc booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus (see Section 8.7).

Following ongoing participants will not be eligible to receive the ad hoc booster vaccination:

Group 5 participants (all cohorts) who crossed over from placebo to receive Ad26.COV2.S at the $5x10^{10}$ vp dose level (ie, placebo crossover vaccination) (see Section 1.3.7).

Group 5 participants (all cohorts) who did not opt for the placebo crossover vaccination and therefore have not received any vaccination with the Ad26.COV2.S vaccine.

Cohort 2 participants who will receive a booster vaccination according to their initial schedule at 6 and 12 months after the primary regimen (Groups 2 and 3, respectively) (see Section 4.1).

Applicable to Belgium only: Per the Belgian-specific protocol Amendment 15, participants aged <65 years enrolled at Belgian sites.

Procedures for Participants Receiving a Single Ad Hoc Booster Dose of $5x10^{10}$ vp Ad26.COV2.S

Vaccination will be planned during the ad hoc booster vaccination visit as soon as the site is operationally ready and the participant has met the length of time requirements from last vaccination (see details above). During this visit, the investigator should ask the participant if he/she received any other COVID-19 vaccine and record type and date of administration.

A urine pregnancy test will be collected from all women of childbearing potential (Cohort 1 and 2 only) and a blood sample for a platelet count (as part of a complete blood count if applicable) will be collected from all participants prior to and 28 days post ad hoc booster vaccination. Vaccination will be performed by a trained and qualified blinded study nurse, medical doctor, or otherwise qualified HCP. Participants will remain under observation at the study site for at least 15 minutes for the presence of any acute reactions. Solicited AEs, collected through a diary, will be recorded from the time of ad hoc booster vaccination until 7 days post-vaccination. All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported from the

time of ad hoc booster vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe of >28 days after previous study vaccination, which are ongoing on the day of the subsequent visit, should be recorded as such. SAEs and COVID-19-like signs and symptoms (refer to Section 8.1.2) will be reported from the time of booster vaccination till the end of booster follow-up/early withdrawal. In addition, AESIs will be reported until the end of booster follow-up/early withdrawal. At that time, the participant will visit the site with regards to AESI and SAE collection, after which the participant will be considered to have completed the study.

Venous blood samples will be collected for assessment of humoral or cellular immune responses from a subset of participants prior to and 28 days, and 6 months post ad hoc booster vaccination (see SoA in Section 1.3.10 for details).

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 14 provides the probabilities of observing at least one AE at given true AE rates.

Table 14: 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[a]: 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 from participants with natural infection occurring after screening (if applicable) will be excluded from the analysis.

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.

[a] If a participant would be vaccinated out of window due to a study pause (per Section 6.9), this will not by default be a reason for excluding this participant from the PPI. A sensitivity analysis might also be performed. Further details will be described in the Statistical Analysis Plan.

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, an AESI, 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 and/or tabulated 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) and LNA immune 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 9. Additional interim analyses may be conducted by the sponsor as needed.

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 the study 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 the study 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; 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

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

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. These interim analyses will present the data in a group-level unblinded fashion, as follows:

- The interim analysis of the first booster vaccination (at 6 months for Cohort 2a or at 8 months for Cohort 2b), will keep the groups 1, 3, and 4 pooled.
- The interim analysis of the second booster vaccination (at 12 months for Cohort 2a or at 14 months for Cohort 2b), will keep the groups 1 and 4 pooled.

This stepwise group-level unblinding approach avoids indirect unblinding of individual participants who have yet to receive the active (or last) booster (eg, due to rare or unique events).

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 the study 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

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

discontinued the study 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; 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.

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 the study earlier.

Planned Analyses: General Considerations

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.

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

Analysis and Reporting of Unblinded Data

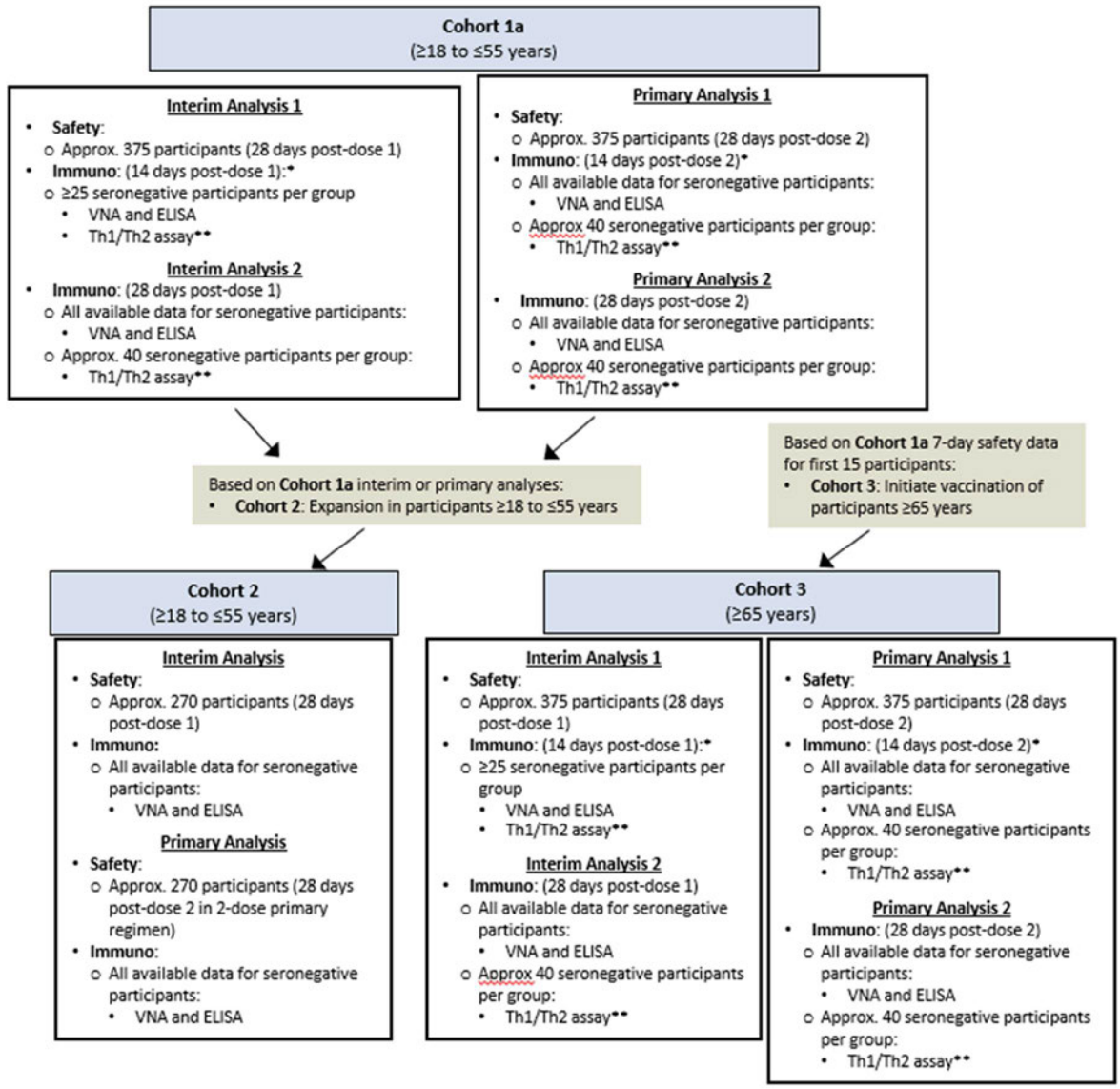
Selected available group unblinded immunogenicity data and blinded safety data from the interim analysis of Cohorts 1a, 1b, and 3 will be published. Following the 7-day post-vaccination 2 safety data being available in Cohorts 1a, 1b, and 3, the sponsor will be unblinded for these cohorts, except for sponsor personnel directly involved with the study site for assessment of safety. Participants, clinical staff, and study-site personnel will remain blinded to the study vaccine allocation.

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.

Following Emergency Use Authorization (EUA), conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S and local approval of protocol Amendment 10 by both Health Authority (HA) and Independent Ethics Committees (IEC)/Institutional Review Board (IRB), a single dose of 5×10^{10} vp Ad26.COV2.S will be offered to enrolled participants who initially received placebo only, resulting in de facto unblinding of

participants and investigators. A stepwise group-level unblinding approach will be used for Cohort 2 to avoid indirect unblinding of individual participants.

Figure 9: 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

9.6. Analyses for Participants Requesting Unblinding to Receive an Authorized/Licensed COVID-19 Vaccine

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

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no clinical data on the safety of receiving a different COVID-19 vaccine after receiving Ad26.COV2.S. In the event of a participant unblinding to receive an authorized/licensed COVID-19 vaccine and the participant received an authorized/licensed COVID-19 vaccine outside of the study, no further study vaccination will be permitted[a]. Unblinded participants, whether in the vaccine or control group that did not receive an authorized/licensed COVID-19 vaccine outside of the study, will be asked to continue to be followed in this study in line with the SoA to the extent that they permit, including Cohort 2 booster vaccinations. Safety and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible.

Procedures installed at the time of unblinding all participants after EUA or approval in any country and local approval of protocol Amendment 10 (refer to Section 8.6), will also apply to participants who were unblinded at their own request prior to Amendment 10. The statistical analyses will follow the same approach as outlined in Section 9.7. The only exception is for Cohorts 2a and 2b participants: if unblinding occurs at their request, they are likely to be completely unblinded, implying they would know in advance whether they would receive active vaccine or placebo at each of the booster time points. These participants will therefore not be included in any of the post-booster safety or efficacy analyses of Cohorts 2a and 2b. If they continue with the booster vaccinations and all study procedures as described in the SoA, they will be included in the immunogenicity analysis.

9.7. Analyses after Unblinding all Participants Following EUA or Approval in any Country

9.7.1. Cohorts 1a, 1b, and 3

The participants in these cohorts have completed the planned study vaccination regimen by the time of unblinding (or have discontinued earlier). In general, after unblinding, participants who received placebo only during primary regimen, can elect to receive a single dose of

[a] Following local approval of protocol Amendment 15, participants who received an authorized/licensed COVID-19 vaccine outside of the study are allowed to receive a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp) if the last vaccination was ≥6 months ago.

$5x10^{10}$ vp Ad26.COV2.S offered at the study site, can opt to receive an authorized/licensed COVID-19 vaccine outside of the study, or may choose not to receive any additional vaccinations. Participants who already received active vaccine will be asked to continue the study or can opt to receive an authorized/licensed COVID-19 vaccine outside of the study.

The safety analyses will be censored at the date of unblinding or the receipt of an unscheduled vaccine[a], whichever event occurs first. SAEs and AESIs reported after unblinding or receipt of an unscheduled vaccine, whichever comes first, will be listed.

The immunogenicity analyses will be censored at the date of the receipt of an unscheduled vaccine. Immunogenicity samples taken after the receipt of an unscheduled vaccine will be included in the listings and flagged. Samples obtained from unblinded participants who do not get any further vaccination, will not be censored from the analyses.

Efficacy analyses will be censored at the date of unblinding or the receipt of an unscheduled vaccine, whichever comes first.

9.7.2. Cohorts 2a and 2b

The participants in Cohorts 2a and 2b will not have completed the planned vaccination schedule by the time of unblinding, because the booster vaccinations will not yet have occurred.

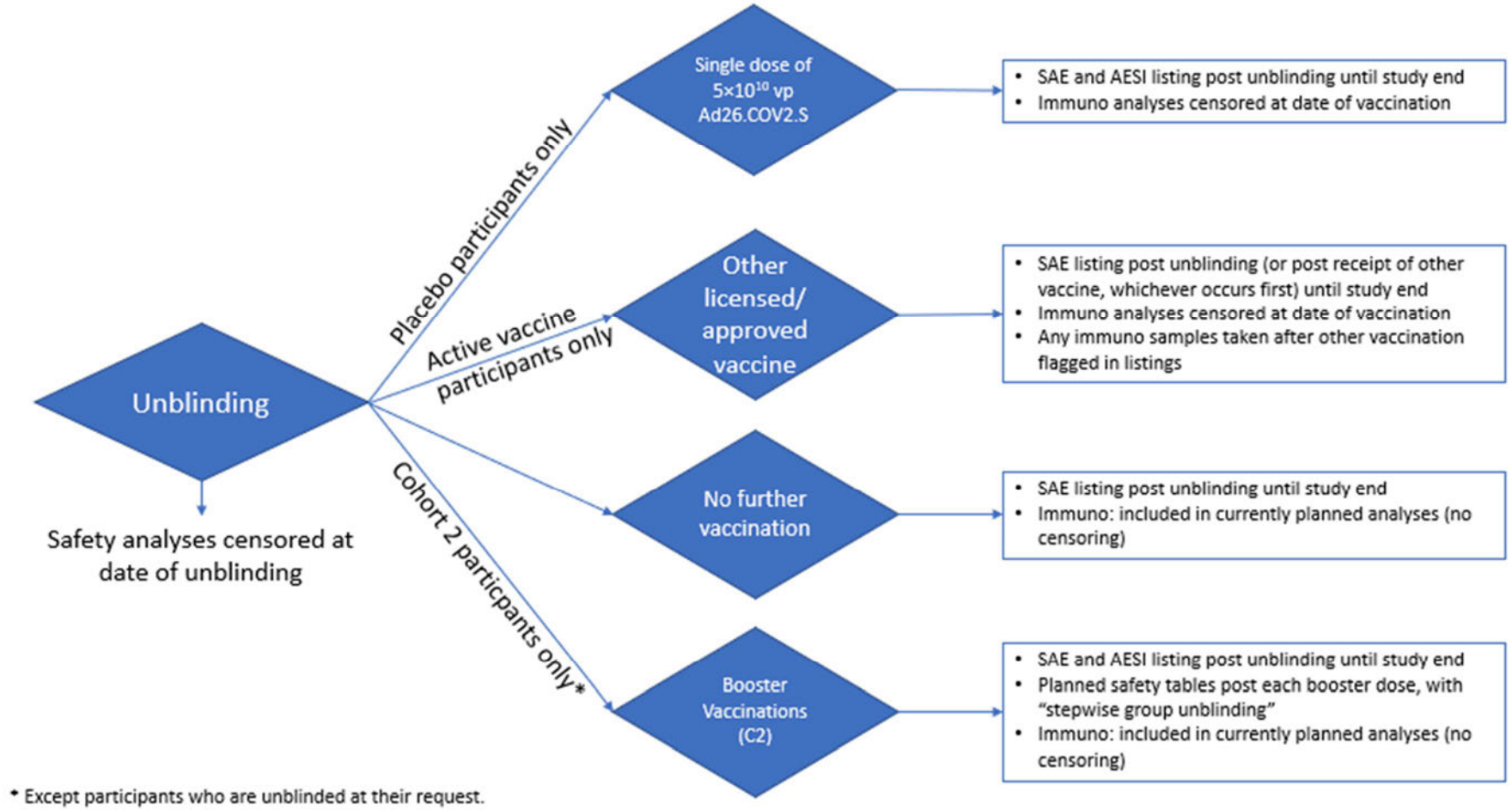
For safety, efficacy, and immunogenicity, the same analysis strategy will be applied as for Cohorts 1a, 1b, and 3.

Analyses pertaining to the booster vaccinations will be produced as planned. The analyses will include all available participants who have followed the vaccination schedules as per the study design (ie, did not receive an unscheduled vaccination). Note that the post-booster safety or efficacy analyses will not include participants who were unblinded at their own request, since they are likely to be completely unblinded (implying they would know in advance whether they would receive active vaccine or placebo at each of the booster time points). Participants who continue with the booster vaccinations and all study procedures as described in the SoA, will be included in the immunogenicity analysis.

The analysis strategy is depicted graphically in Figure 10.

[a] Unscheduled vaccination: for placebo participants: a single dose of $5x10^{10}$ vp Ad26.COV2.S offered at the study site or an authorized/licensed COVID-19 vaccine offered outside of the study; for participants in the active vaccine groups: an authorized/licensed COVID-19 vaccine offered outside of the study.

Figure 10: Analysis strategy after unblinding, depicted by scenario



AESI adverse event of special interest; C cohort; SAE serious adverse event

9.8. Analysis After Receipt of the Ad Hoc Booster Vaccination

Amendment 15 of this protocol offers eligible study participants (see Section 5) a single ad hoc booster vaccination with the Ad26.COV2.S vaccine at the 5×10^{10} vp dose level. The main analyses will be conducted as described in Section 9.7, in which censoring is applied for the various statistical analyses depending on the date of unblinding or receipt of an unscheduled vaccine. In addition, receipt of the ad hoc booster vaccination will also be a reason for censoring data from the main analyses.

For safety and reactogenicity, additional analyses will be conducted on study participants who received the ad hoc booster vaccination. Safety and reactogenicity analyses will be presented from the start of the ad hoc booster vaccination until 7 days post vaccination for reactogenicity, until 28 days post vaccination for unsolicited AEs, and until the end of the study for SAEs and AESIs.

For immunogenicity, an additional analysis will be conducted on study participants who received the ad hoc booster vaccination. Immunogenicity analyses will be presented from the start of the ad hoc booster vaccination and will show their immune responses at each subsequent time point, as available.

The analyses will be descriptive, presenting study participants according to their original vaccination regimen. In addition, the analyses may also be conducted separately by subgroups of study participants who received a COVID-19 vaccine outside of the study versus study participants who did not receive a COVID-19 vaccine outside of the study. Additional exploratory analyses may be conducted.

Details for the analysis of the ad hoc booster vaccination will be provided in an amendment to the study Statistical Analysis Plan.

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
AESI	adverse event of special interest
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
CLS	capillary leak syndrome
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
EUA	emergency use authorization
FAMHP	Federal Agency for Medicines and Health Products
FAS	full analysis set
FDA	Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
FOIA	Freedom of Information Act
FU	follow-up
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
HIT	heparin-induced thrombocytopenia
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
LNA	lymph node aspirate
mRNA	messenger ribonucleic acid
MedDRA	Medical Dictionary for Regulatory Activities

MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
mo	month(s)
MSD	Meso Scale Discovery
PBMC	peripheral blood mononuclear cell
PF4	platelet factor 4
PI	principal investigator
PPE	per protocol efficacy
PPI	per protocol immunogenicity
PQC	product quality complaint
RBD	receptor-binding domain
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse-transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
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
TTS	thrombosis with thrombocytopenia syndrome
vac	vaccination
VNA	virus neutralization assay
vp	virus particles
WHO	World Health Organization

10.2. Appendix 2: Clinical Laboratory Tests

10.2.1. All Cohorts

The following tests will be performed at screening, vaccination 1 and 2 visits, and 7 days after each vaccination 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>

10.2.2. Additional Hematology and Coagulation Testing

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	Timepoints
Testing done locally	Whole blood sample for platelet count which at some sites may be part of a complete blood count with differential	• Pre-vaccination with Ad26.COV2.S in participants from Cohort 2 that will receive booster vaccinations, for Group 5 placebo participants receiving a single dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or approval in any country, and for all eligible participants (see Section 8.7) receiving a single ad hoc booster dose of $5x10^{10}$ vp Ad26.COV2.S after approval of protocol amendment 15. • As part of a suspected AESI investigation if applicable (any Cohort)
Testing done centrally	Serum/plasma samples for coagulation-related assays such as but not limited to: • Activated partial thromboplastin time • Prothrombin time • International normalized ratio • Fibrinogen • D-dimer • Lupus anticoagulant • Anti-cardiolipin antibody • Beta-2 glycoprotein· • Heparin Induced Thrombocytopenia (HIT)/PF4 Ab, IgG·(HIT assay) • Platelet activation assay (if HIT/PF4 is positive) • Homocysteine • ADAMTS13 Activity and Inhibitor Profile	Based on the clinical evaluation of the suspected AESI (eg, whether thrombocytopenia is observed in conjunction with a thrombotic event), all or some of these tests may be conducted on the stored pre-vaccination sample (retrospective test) and on the samples obtained as part of the AESI investigation, upon discretion of the sponsor. Similar samples from appropriate controls (from vaccinated participants who did not experience an AESI) within the study may be used as part of investigation of AESIs.

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. Participants will be reconsented, including, but not limited to the following cases:

Group 5 placebo participants receiving a single dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or approval in any country.

Participants from Cohort 1a, 1b, and 3 who wish to participate in the additional follow-up after local approval of protocol amendment 14.

Participants receiving a single ad hoc booster dose of $5x10^{10}$ vp Ad26.COV2.S after local approval of protocol amendment 15.

All Cohort 1b participants will be offered participation in an optional fine needle LNA procedure, for which they will have to sign an additional ICF. The participant will be asked to sign and personally date an ICF indicating agreement to participate in the LNA procedure. Refusal to participate in the optional procedure will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

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.

AESI Adjudication Committee

An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS (see Section 8.3.6). A Charter will be developed to describe the roles and responsibilities of the Committee.

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. Documentation of recommended procedures for (a)symptomatic COVID-19 participants with RT-PCR confirmed SARS-CoV-2 infection (refer to Sections 8.1.2 and 8.1.3), will be added to the 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, Adverse Events of Special Interest, 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. In general, (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.

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.

Adverse Events of Special Interest

AESIs will be carefully monitored during the study by the sponsor. Suspected AESIs must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious AEs) or causality assessment, following the procedure described above for SAEs and will require enhanced data collection.

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.

AEs Related to the Optional Lymph Node Aspiration Procedure

AEs and relevant concomitant therapies occurring during the optional LNA study period will be collected in the eCRF if related to study procedures or if serious or AESI be reported to the sponsor according to SAE/AESI requirements.

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,[46] included in Section 10.6, Appendix 6, Toxicity Grading Scale.

The AESI definition includes thrombocytopenia, defined as platelet count <150,000/µL as per the Brighton Collaboration (Section 8.3.6.1).

For the purpose of severity grading, an AE of thrombocytopenia based on platelet counts >140,000/µL and <150,000 µL should be considered Grade 1.

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

For participants who provided consent for the optional LNA procedure, AEs related to this procedure will be collected as indicated in Section 8.1.1.1.

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.

Adverse Events of Special Interest

Adverse events of special interest will be carefully monitored during the study by the sponsor. These events must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious AEs) or causality following the procedure described above for SAEs and will require enhanced data collection.

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

[#] Revised by the sponsor.

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

Case Definition for Severe/Critical COVID-19

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

[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 8.1.1.1).

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 ³ 30 breaths/minute, heart rate ³ 125 beats/minute, oxygen saturation (SpO_2) ≤93% on room air at sea level*, or partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg)

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

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[13] (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 8.1.1.1).

- COVID-19 symptoms consistent with those defined by the US FDA harmonized case definition[13] 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 8.1.2.3),

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.

The recommended procedure for participants with asymptomatic COVID-19 RT-PCR confirmed infection is detailed in Section 8.1.3.

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: Summary of Guidance from CDC Website on Underlying Medical Conditions That Lead or Might Lead to Increased Risk for Severe Illness From COVID-19

People of any age with **certain underlying medical conditions** are at increased risk for severe illness from COVID-19:

People of any age with the following conditions **are at increased risk** of severe illness from COVID-19:

- Cancer
- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Immunocompromised state (weakened immune system) from solid organ transplant
- Obesity (body mass index [BMI] of 30 or higher)
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease
- Type 2 diabetes mellitus

COVID-19 is a new disease. Currently there are limited data and information about the impact of underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we know at this time, people with the following **conditions might be at an increased risk** for severe illness from COVID-19:

- Asthma (moderate to severe)
- Cerebrovascular disease (affects blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension or high blood pressure
- Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
- Neurologic conditions, such as dementia
- Liver disease
- Pregnancy
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Smoking
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC AA refVal=https%3A%2F%2Fwww.cdc.gov%2 Fcoronavirus% 2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. Accessed: 13 July 2020.

10.11. Appendix 11: TTS AESI Form

The form below represents the type of information that may be collected in case of a suspected AESI to help adjudicate whether the event is a case of TTS. Additional data may be requested by the sponsor for investigation of the event.

Adverse Event of Special Interest Questionnaire (AESIQ) for Thromboembolism with Thrombocytopenia Syndrome

Date of Report: [dd-MMM-yyyy]

1. Adverse Event Description

Participant's clinical signs and symptoms

☐ Leg/Calf Oedema	☐ Pain in Leg/Calf	☐ Haemoptysis
☐ Dyspnoea	☐ Chest Pain/Discomfort	☐ Syncope
☐ Tachypnoea	☐ Tachycardia	☐ Cough
☐ Loss of consciousness	☐ Headache	☐ Seizure
☐ Visual impairment	☐ Weakness	☐ Impaired speech
☐ Confusional state	☐ Paresthesia	☐ Gait disturbance

☐ Other symptoms:

Was patient on VTE prophylaxis? ☐ No ☐ Yes, details:

2. Medical History and Concurrent Conditions
Provide details:

Is the participant overweight or have obesity?	☐ No ☐ Yes
If available, please provide: Height	Weight BMI
Does the participant have a sedentary lifestyle[a]?	☐ No ☐ Yes – details:
Has the participant been in a sitting position for long periods of time prior to the event?	☐ No ☐ Yes – details:
Is there a current history of smoking (active or passive)?	☐ No ☐ Yes – details:
Is there a prior history of smoking (active or passive)?	☐ No ☐ Yes – details:
Does the participant have a prior history of:	
Cancer	☐ No ☐ Yes – details:
Autoimmune disease (i.e., collagen-vascular disease, inflammatory bowel disease) or myeloproliferative disease?	☐ No ☐ Yes – details:
Clotting disorder or a hypercoagulable state	☐ No ☐ Yes – details:
Varicose veins	☐ No ☐ Yes – details:
Trauma to the involved leg or pelvis	☐ No ☐ Yes – details:
DVT/PE or other VTE	☐ No ☐ Yes – details:
Blood transfusion	☐ No ☐ Yes – details:
Cardiovascular disease	☐ No ☐ Yes – details:

[a] Any waking behavior characterized by an energy expenditure less than or equal to 1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture

If the participant has experienced a previous thrombotic event, address the following:
1. Date (or estimate) 2. Provide brief description of the nature of the event 3. Provide brief description of the treatment of the event 4. Note any residual manifestations of the event.

If the patient has experienced more than one previous thrombotic event, please list other events.

Was the (female) participant pregnant at the time of event? ☐ No ☐ Yes – details:

Does the participant has any of genetic risk factors:

☐ Dysfibrinogenemia ☐ Antiphospholipid syndrome ☐ Factor V Leiden mutation
☐ Protein C or S deficiency ☐ Elevated factor VIII levels ☐ Anti-thrombin deficiency
☐ Hyperhomocysteinemia ☐ Prothrombin gene mutation ☐ Blood-clotting disorder
☐ Thrombophilia

Does the participant have any acquired risk factors:

☐ Reduced mobility (paralysis, paresis, travel etc.) ☐ Recent surgery
☐ Indwelling central venous catheters ☐ Recent trauma
☐ Recent discontinuation of anticoagulants (e.g., heparin, warfarin, DOACs)
☐ Hormone replacement therapy (including contraceptives)
☐ Phlebitis ☐ Lupus
☐ Inflammatory bowel disease ☐ Myeloproliferative disorders
☐ Diabetes mellitus ☐ Hyperlipidemia
☐ Hypertension ☐ Dehydration
☐ Other significant medical co-morbidities or risk factors for DVT, specify:

If yes to any of the above, provide details:
Provide Well's score, if calculated:

3. **Relevant results of diagnostic tests including laboratory tests, imaging, biopsies, etc.** (Note the levels/conclusion, date performed, **normal ranges** as well as any other details. **Alternatively, attach full reports of the diagnostic tests.)**

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
CBC with smear (microscopic evaluation)		
ESR		
Platelet count		
Antibodies to platelet factor 4 (PF4)		
Fibrinogen levels		
Clauss fibrinogen assay		

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
D-Dimer		
Clotting Profile (PT, aPTT- prior to an anticoagulation treatment)		
Thrombin time (Bovine) Plasma		
Prothrombin		
Antithrombin activity		
Factor V Leiden		
Protein C activity		
Protein S activity		
C-reactive protein		
Homocystein levels		
Dilute Russells Viper Venom Time (DRVVT), Plasma		
Activated Protein C Resistance V (APCRV), Plasma		
Thrombophilia interpretation		
Anticardiolipin antibodies (IgG and IgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (IgG and IgM)		
Lupus anticoagulant		
Heparin antibodies		
ANA and ANCA		
IL6 levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
MethylenetetraHydrofolate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain Natriuretic Peptide		
Arterial Blood Gases		

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
Chest X-Ray		
Electrocardiography		
Echocardiography		
Duplex Ultrasonography		
MRI scan		
CT scan		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Provide details of any additional diagnostic results:

10.12. Appendix 12: Thrombotic Events to be Reported as AESIs

At the time of protocol Amendment 11 writing, the list of thrombotic events to be reported to the sponsor as AESIs is provided below. Further guidance may become available on thrombotic events of interest.

- MedDRA PTs for large vessel thrombosis and embolism:
  - Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis

- MedDRA PTs for more common thrombotic events:
  - Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction*, MedDRA PTs for stroke*

Source: Shimabukuro T. CDC COVID-19 Vaccine Task Force. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices (ACIP). April 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html.

*Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 29 January 2021) https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 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.

Section Number and Name	Description of Change	Brief Rationale
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.

Section Number and Name	Description of Change	Brief Rationale
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.
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.

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.

Amendment 7 (03 November 2020)

Overall Rationale for the Amendment: In this amendment, the mitigation strategy after a study pause is clarified. Additional changes are listed below.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 8 STUDY ASSESSMENTS AND PROCEDURES 9.3 Populations for Analysis Sets	Clarified that efforts will be made to still vaccinate a participant if the vaccination window is missed due to a study pause. Clarified that these participants will not be excluded from the PPI by default for this reason.	Mitigation in case of study pause: clarification on out of window vaccination.
6.9 Study Vaccination Pausing Rules	Text added to state that this study will also be paused if a pausing rule is met in studies COV1002, COV2001, or COV3001.	Mitigation in case of study pause: additional safety measure.
8.1.2.1 Prespecified Criteria for Suspected COVID-19	It has been clarified that because several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events.	To ensure that vaccine-related events do not trigger the COVID-19 related follow-up procedures for mild disease, to be able to include cases of moderate disease that were not classifiable by the definition and for simplification and clarification purposes.
8 STUDY ASSESSMENTS AND PROCEDURES	It has been added that serology testing outside the study is discouraged and if testing would be needed, the site will guide the participant to an appropriate assay.	Vaccination with Ad26.COV2.S may interfere with some serologic assays utilized at local community health clinics/commercial laboratories and may result in unblinding the participant.
8 STUDY ASSESSMENTS AND PROCEDURES	It has been clarified that the participant will be notified of a confirmed positive SARS-CoV-2 infection and positive serology test.	For clarification purposes.
5.2 Exclusion Criteria	A note regarding the use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S, has been added to Exclusion Criterion 9 for clarification purposes.	For clarification purposes.
2.3.1 Risk Related to Study Participation	Inconsistencies were corrected.	Correction of inconsistencies.
Title page	Prepared by line removed.	To align with internal guidelines on legal entity to be mentioned on title page.

Amendment 8 (08 December 2020)

Overall Rationale for the Amendment: In this amendment, a recommendation to the protocol was added regarding additional follow-up procedures for participants with (a)symptomatic COVID-19 RT-PCR confirmed infection.

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 8.1.3 Procedures in Case of Asymptomatic COVID-19 RT-PCR Confirmed Infection 10.3.10 Source Documents 10.8.4 Case Definition for Asymptomatic or Undetected COVID-19	A recommendation was added to the protocol regarding procedures in case of (a)symptomatic COVID-19 RT-PCR confirmed infection. These participants are recommended to be followed until 2 consecutive negative nasal swabs can be obtained.	To ensure the safety of people that are in contact with these participants and to be able to include the data from participants with asymptomatic COVID-19 RT-PCR confirmed infection in efficacy evaluations.
9.5 Planned Analysis	Text was revised to clarify that at the time of the interim analysis, the sponsor will be unblinded for cohorts 1a, 1b, and 3, except for sponsor personnel directly involved with the study site.	Clarification added regarding the unblinding of the data at the time of the interim analysis.
1.3 Schedule of Activities (SoA) (and subsections) 7.1 Discontinuation of Study Vaccination 7.2 Participant Discontinuation/Withdrawal From the Study	Clarified that participants who no longer wish to receive study vaccination will be offered safety and immunogenicity follow-up. Participants who wish to withdraw consent from participation in the study will be offered an optional visit for safety follow-up.	Clarification added for participants who do not wish to receive the second vaccination or who wish to withdraw consent.
8 Study Assessments and Procedures	On-site serologic testing will be offered upon participant's request at the next scheduled blood draw visit.	To avoid participants being unblinded by serologic testing organized outside the study.
4.2 Scientific Rationale for Study Design 8.5 Biomarkers	For all participants, biomarker analysis (PAXgene, RNA-seq) will be performed to explore potentially informative biomarkers related to vaccine immunogenicity and SARS-CoV-2 infection (including relations with COVID-19 disease severity).	Alignment with Phase 3 protocols.

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	• Clarified that non-immunomodulator treatment is allowed as well as steroids at a non-immunosuppressive dose or route of administration. • Added that a substantial immunosuppressive steroid dose is defined as ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent. Therefore, the specification of '(>10 days)' when referring to the chronic use of systemic corticosteroids has been removed from the exclusion criterion 4 and aligned throughout.	Alignment with Phase 3 protocols.
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	Clarified that the use of investigational immunoglobulin (Ig) and monoclonal antibodies or convalescent serum are not allowed during the study.	Alignment with Phase 3 protocols.
5.2 Exclusion Criteria	Clarified that a serological test for SARS-CoV-2-specific antibodies should be performed at screening.	Clarification.
5.2 Exclusion Criteria	Updated the list of conditions that increase the risk of progression to severe COVID-19.	Alignment with Phase 3 protocols.
5.2 Exclusion Criteria	Gestational diabetes has been removed from the list of comorbidities (or risk factors) that might be associated with increased risk of progression to severe COVID-19 as pregnant women are not allowed to participate.	Gestational diabetes is not applicable in the current study as pregnant women are not allowed to participate.
5.2 Exclusion Criteria 6.6 Continued Access to Study Vaccine After the End of the Study	It has been clarified that the sponsor will look into the possibility of offering placebo recipients the study vaccine, if this vaccine is determined to be efficacious, considering country-specific conditions and ethical considerations.	Alignment with Phase 3 protocols.
10.4.1 Adverse Event Definitions and Classifications	Section updated to clarify that (S)AEs caused by molecularly confirmed SARS CoV 2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately.	Alignment with Section 9.4.2.
4.1 Overall Design	Sentence about the procedure for participants not receiving the second vaccination was removed, because it was explained more correctly in the footnote underneath.	Alignment with footnote table 2.
6.7 Treatment of Overdose	Definition of what can be regarded as an overdose was corrected.	Correction of inconsistency
10.8.1 Appendix 8: Case Definition for Moderate to Severe COVID-19	It has been clarified that the adjustment according to altitude for the SpO_2 criteria is per the investigator judgement.	Clarification

Section Number and Name	Description of Change	Brief Rationale
6.3 Measures to Minimize Bias: Randomization and Blinding	Immunogenicity follow-up was added to the allowed safety follow-up for participants who had their intervention assignment unblinded.	Clarification
9.3 Populations for Analysis Sets	Though samples obtained after missed vaccinations or after natural infection will not be analyzed, the participants remain included in the PPI.	Clarification

Amendment 9 (18 December 2020)

Overall Rationale for the Amendment: In this amendment, language was included regarding unblinding of study participants who may become eligible to receive an authorized/licensed COVID-19 vaccine during the course of the study.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities (SoA) 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine After the End of the Study 7.1 Discontinuation of Study Vaccination 9.6 Analyses for Participants Unblinded Due to Administration of an Authorized/Licensed COVID-19 Vaccine	Clarification of procedures for unblinding of study participants who may become eligible to receive an authorized/licensed COVID-19 vaccine during the course of the study.	To ensure that if participants become eligible to receive an authorized/licensed COVID-19 vaccine, they are aware of the potential options and ramifications, including the lack of safety data on receiving two different COVID-19 vaccines.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.1.1 Immunogenicity Assessments 10.1 Appendix 1: Abbreviations	An exploratory humoral immunogenicity endpoint was added: analysis of antibodies binding to SARS-CoV-2 S protein and the receptor-binding domain (RBD) of the SARS-CoV-2 S protein by Meso Scale Discovery (MSD) assay.	To allow for in-depth analysis of the binding antibody generated by Ad26.COV2.S.
9.5 Planned Analysis	Separate headers were added to this section to group information regarding analysis and reporting of unblinded data and general considerations.	To provide oversight and clarity.

Amendment 10 (25 February 2021)

Overall Rationale for the Amendment: The main purpose of this amendment is to outline the procedures to be followed after Emergency Use Authorization (EUA), conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S and local approval of protocol Amendment 10 by both Health Authority (HA) and Independent Ethics Committees (IEC)/Institutional Review Board (IRB), when a single dose of 5×10^{10} vp Ad26.COV2.S will be offered to enrolled participants who initially received placebo only, resulting in de facto unblinding of participants and investigators.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.7 Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or Approval in any Country 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5.5 Criteria for Temporarily Delaying Administration of Study Vaccination 6.3 Measures to Minimize Bias: Randomization and Blinding 6.1 Study Vaccinations Administered 6.6 Continued Access to Study Vaccine After the End of the Study 7.1 Discontinuation of Study Vaccination 7.2 Participant Discontinuation/Withdrawal from the Study 7.4 Discontinue from Placebo Group Participation 8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting 8.6 Assessments and Procedures after Emergency Use Approval	Following Emergency Use Authorization, conditional licensure, or approval in any country for the single-dose regimen of 5×10^{10} vp Ad26.COV2.S, all participants from countries where Amendment 10 is locally approved by the Health Authority and IEC/IRB will be unblinded to disclose who received placebo only during primary regimen.	To avoid participants in the active vaccine groups from requesting unblinding in order to receive an authorized/licensed COVID-19 vaccine and to enable participants in the placebo groups to receive a single dose of 5×10^{10} vp Ad26.COV2.S.
	After unblinding, a single dose of 5×10^{10} vp Ad26.COV2.S will be offered to enrolled participants who received placebo only during primary regimen. If willing to receive, they will discontinue from participation in the placebo groups.	Keeping participants on placebo during a pandemic while authorized vaccines have become available is not sustainable and cannot be defended from an ethical point of view.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.2 Scientific Rationale for Study Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.5 Planned Analysis 9.6 Analyses for Participants Requesting Unblinding in order to Receive an Authorized/Licensed COVID-19 Vaccine 9.7 Analyses after Unblinding all Participants Following EUA or Approval in any Country	All data will be analyzed separately from the point of unblinding.	Statistical analysis is impacted by the unblinding and needs to be updated.
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine After the End of the Study 7.1 Discontinuation of Study Vaccination 9.6 Analyses for Participants Requesting Unblinding in order to Receive an Authorized/Licensed COVID-19 Vaccine	Procedures and analyses installed at the time of unblinding all participants after Emergency Use Authorization or approval in any country, and local approval of protocol Amendment 10, will also apply to participants who were unblinded at their own request prior to Amendment 10.	Clarification.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Analysis of neutralizing and binding antibodies against emerging SARS-CoV-2 virus lineages has been added to exploratory endpoints.	To accommodate for additional research regarding the new emerging SARS-CoV-2 virus variants.
6.9 Study Vaccination Pausing Rules	The prespecified pausing criteria will no longer be in place to trigger a study pause upon completion of all Day 57 vaccinations in all cohorts.	This additional safety measure is no longer applicable at the stage of booster vaccination administration.
1.3 Schedule of Activities (SoA)	Footnotes with regards to the 1-hour post-vaccination observation were also added to vital signs to emphasize that vital signs need to be checked at the end of the observation period.	Clarification.
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	Long-term sequelae of COVID-19 (eg, anosmia, headache, fatigue, and other symptoms at the investigator's judgement) will not be followed until their resolution if not resolved within a month.	Clarification and alignment.

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	If the first nasal swab is negative, collection of data will continue until the negative test is confirmed by the second nasal swab or until sign and symptom resolution, whichever comes first.	Clarification and alignment.
1.3 Schedule of Activities (SoA) 6.8 Prestudy and Concomitant Therapy	It was added that receipt of a licensed COVID-19 vaccination should be recorded at any timepoint during the study.	Clarification and alignment.
1.1 Synopsis 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms 8.1.3 Procedures in Case of Asymptomatic COVID-19 RT-PCR Confirmed Infection	An additional paragraph from the protocol body was copied into the synopsis and some additional minor clarifications were added.	Clarification.
1.1 Synopsis 1.2 Schema 1.3.4 Cohort 2b 4.1 Overall Design 8 STUDY ASSESSMENTS AND PROCEDURES	Footnotes directing participants in Cohort 2b who missed the Day 57 vaccination have been corrected to align with Section 7.2 of the protocol.	Correction of inconsistency.
2.2 Background 2.3.1 Risks Related to Study Participation 2.3.2 Benefits of Study Participation	Ad26.COV2.S safety and efficacy data acquired from primary/interim analyses of ongoing clinical studies have been updated in line with the current IB.	To update information.
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Addition of minor clarifications. Alignment across sections in the protocol.

Amendment 11 (6 May 2021)

Overall Rationale for the Amendment: This amendment has been created to include additional safety measures due to reports of adverse events following use of the Ad26.COV2.S vaccine under emergency use authorization in the US, suggesting an increased risk of thrombosis combined with thrombocytopenia. Based on this, thrombosis with thrombocytopenia syndrome (TTS), which is a very rare event, will be followed in this protocol as adverse event of special interest (AESI) that needs to be reported to the sponsor within 24 hours of awareness. In addition, anaphylaxis has been added as an important identified risk.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.3.2 Booster Vaccination Cohort 2a 1.3.4.2 Booster Vaccination Cohort 2b 1.3.7 Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or Approval in any Country 1.3.8 Procedures for Participants with a Suspected AESI 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.4 End of Study Definition 6.8 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.4 Clinical Laboratory Assessments 8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 8.3.2 Method of Detecting Adverse Events, and Serious Adverse Events, and Adverse Events of Special Interest 8.3.3 Follow-up of Adverse Events, and Serious Adverse Events, and Adverse Events of Special Interest 8.3.6 Adverse Events of Special Interest 8.6 Assessments and Procedures after EUA or Approval in any Country 9.4.2 Primary Endpoints 10.1 Appendix 1: Abbreviations 10.2 Appendix 2: Clinical Laboratory Tests 10.4.1 Adverse Event Definitions and Classifications 10.4.5 Procedures	Thrombosis with thrombocytopenia syndrome (TTS) will be considered an adverse event of special interest (AESI). Follow-up assessments will be performed in the event of a suspected AESI.	Emerging data following use of the Ad26.COV2.S vaccine under emergency use authorization in the US suggest an increased risk of thrombosis combined with thrombocytopenia, with onset of symptoms approximately 1-2 weeks after vaccination. Therefore, additional reporting and data collection procedures are implemented to detect and follow-up thrombotic events and thrombocytopenia and identify cases of TTS.

Section Number and Name	Description of Change	Brief Rationale
10.11 Appendix 11: TTS AESI form 10.12 Appendix 12: Thrombotic Events to be Reported as AESIs 11 REFERENCES		
2.3.1 Risks Related to Study Participation	Side effects were updated to include injection site pain and nausea. It has been clarified that anaphylaxis is considered an important identified risk.	To align with the vaccine's risk language. Added anaphylaxis as identified risk.
1.3 Schedule of Activities (SoA) 7.2 Participant Discontinuation/Withdrawal From the Study	Clarify that an early exit visit is not required for participants that are lost to follow-up or have died.	Prevent protocol deviations.
Throughout the protocol	Minor updates.	Minor updates.

Amendment 12 (27 May 2021)

Overall Rationale for the Amendment: This amendment was created to clarify that suspected adverse events of special interest (AESIs) should be reported for all participants after local approval of protocol Amendment 11. Additional changes are listed below.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 Cohort 1a 1.3.2 Cohort 1b 1.3.3.2 Booster Vaccination Cohort 2a 1.3.4.2 Booster Vaccination Cohort 2b 1.3.5 Cohort 3 1.3.7 Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S after EUA or Approval in any Country 3 OBJECTIVES AND ENDPOINTS 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Clarified that suspected AESIs should be reported for all participants after local approval of protocol Amendment 11.	Clarification.
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 8.6 Assessments and Procedures after EUA or Approval in any Country 9.6 Analyses for Participants Requesting Unblinding to Receive an	It was clarified that unblinded participants (active or placebo) who did not receive an authorized/licensed COVID-19 vaccine outside of the study will be asked to continue to be followed in this study, including booster vaccinations for Cohort 2 participants.	Clarification.

Authorized/Licensed COVID-19 Vaccine		
6.6 Continued Access to Study Vaccine After the End of the Study 6.8 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination 9.6 Analyses for Participants Requesting Unblinding to Receive an Authorized/Licensed COVID-19 Vaccine	Participants who received an authorized/licensed COVID-19 vaccine outside of the study will be discontinued from vaccination.	Clarification.
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 9.6 Analyses for Participants Requesting Unblinding to Receive an Authorized/Licensed COVID-19 Vaccine	Clarified that there are no clinical data on the safety of receiving a different COVID-19 vaccine after receiving Ad26.COV2.S.	Clarification.
6.3 Measures to Minimize Bias: Randomization and Blinding	Clarified that manual kits may be used if IWRS cannot be updated to allow dispensing of investigational product to Cohort 2 participants who have previously been unblinded but did not receive and authorized/licensed COVID-19 vaccine.	Clarification.
8 STUDY ASSESSMENTS AND PROCEDURES	It was clarified that visit windows for vaccination visits will not apply for study pauses or vaccination pauses.	Clarification.
2.3.1 Risks Related to Study Participation	It was clarified that cases of thrombosis with thrombocytopenia syndrome occurred within the first 3 weeks following vaccination instead of 1-2 weeks following vaccination.	Clarification requested by HA to align with SmPC.
1.1 Synopsis 9.6 Analyses for Participants Requesting Unblinding to Receive an Authorized/Licensed COVID-19 Vaccine 9.7.2	Clarified for that for Cohorts 2a and 2b, if unblinding occurs at the participants request, these participants will not be included in any of the post-booster safety or efficacy analyses of Cohorts 2a and 2b. If they continue with the booster vaccinations and all study procedures as described in the SoA, they will be included in the immunogenicity analysis.	Clarification.
Throughout the protocol	Minor errors and inconsistencies were corrected throughout the protocol.	Correction of minor errors and inconsistencies.

Amendment 13 (04 June 2021**)**

Overall Rationale for the Amendment: This amendment was created to update the blood volume to be drawn in the event of an adverse event of special interest (AESI).

Section Number and Name	Description of Change	Brief Rationale
1.3.8 Procedures for Participants with a Suspected AESI 8 STUDY ASSESSMENTS AND PROCEDURES 10.2.2 Additional Hematology and Coagulation Testing	The total blood volume to be drawn at Day 1 and Day 29 of a suspected AESI is 15 mL, for a total of 30 mL additional blood in the event that a participant experiences a suspected AESI.	Clarification on blood volume collected in the event of an AESI. Appendix was clarified to indicate that testing in the event of a suspected AESI is applicable to all Cohorts.

Amendment 14 (29 July 2021)

Overall Rationale for the Amendment: This amendment was created to add another year of follow-up and its related safety and immunogenicity assessments for Cohorts 1a, 1b and 3 participants in order to collect additional long-term safety and immunogenicity data for more than one year after second vaccination.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design 4.4 End of Study Definition 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.1 Immunogenicity Assessments 8.1.4 Efficacy assessments	One additional year of follow-up and its related safety and immunogenicity assessments for Cohorts 1a, 1b and 3 participants were added. Inclusion of four visits during the additional year of follow-up.	Additional safety and immunogenicity follow-up for two years after second vaccination. To aid in participant retention during the additional follow-up period in the current study.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Updated the time-period of primary objective for safety assessment from 12 months after second vaccination to 24 months after second vaccination.	Update in accordance with the additional year of follow-up.
1.1 Synopsis 9.5 Planned Analysis	Added text regarding the follow-up analysis of the study at 24 months after second vaccination in Cohorts 1a, 1b and 3.	Update in accordance with the additional year of follow-up.
1.3.9 Additional Follow-up for Cohorts 1a, 1b and 3 8 STUDY ASSESSMENTS AND PROCEDURES	The total blood volume to be drawn during the study for Cohorts 1a, 1b and 3 was updated.	Update to the blood volume collected during the additional year of follow-up.
1.3.8 Procedures for Participants with a Suspected AESI	Clarification was added that if an AESI is reported to the investigator, more than 28 days after the onset of the event, AESI Day 29 visit will therefore become redundant and does not need to be performed.	Clarification

1.3.9 Additional Follow-up for Cohorts 1a, 1b and 3 6.8 Prestudy and Concomitant Therapy	Text was added about participants from Cohorts 1a, 1b and 3, who received additional/booster COVID-19 vaccines outside of the study during the additional follow-up of the study, should be allowed to stay in the study (if willing), however these vaccines should be recorded in the Concomitant Medications section of the eCRF.	Clarification
2.3.1 Risks Related to Study Participation 7.1 Discontinuation of Study Vaccination 8.2.1 Physical Examinations 8.6 Assessments and Procedures after EUA or Approval in any Country 10.1 Abbreviations	Text has been added regarding the increased risk of Guillain-Barre Syndrome (GBS) following use of the Ad26.COV2.S vaccine. GBS has also been added to the list of reasons for the discontinuation of the Ad26.COV2.S vaccine. The symptom-directed physical examination will also include basic neurological examination, if warranted.	Based on the emerging data following use of the Ad26.COV2.S vaccine, GBS has been identified as an adverse drug reaction for the use of Ad26.COV2.S vaccine.
7.1 Discontinuation of Study Vaccination 8.6 Assessments and Procedures after EUA or Approval in any Country 10.1 Abbreviations	Capillary Leak Syndrome (CLS) was added to the list of reasons for the discontinuation of the Ad26.COV2.S vaccine.	Based on the emerging data following use of the Ad26.COV2.S vaccine, CLS has been identified as a contraindication for the use of Ad26.COV2.S vaccine.
Throughout the protocol	Minor errors and inconsistencies were corrected throughout the protocol.	Correction of minor errors and inconsistencies.

Amendment 15 (7 October 2021)

Overall Rationale for the Amendment: The main purpose of this amendment is to offer a single ad hoc booster vaccination with Ad26.COV2.S at the $5x10^{10}$ vp dose level to all eligible participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, a messenger ribonucleic acid (mRNA) vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago.

The following ongoing participants will not be eligible to receive this ad hoc booster vaccination:

- Group 5 participants (all cohorts) who crossed over from placebo to receive Ad26.COV2.S at the $5x10^{10}$ vp dose level (ie, placebo crossover vaccination) (see Section 1.3.7).
- Group 5 participants (all cohorts) who did not opt for the placebo crossover vaccination and therefore have not received any vaccination with the Ad26.COV2.S vaccine.
- Cohort 2 participants who will receive a booster vaccination according to their initial schedule at 6 and 12 months after the primary regimen (Groups 2 and 3, respectively) (see Section 4.1).

Rationale: A single dose of Ad26.COV2.S vaccine is immunogenic and highly efficacious against severe COVID-19 disease and COVID-19-related hospitalization and death. Furthermore, while protection against variants of concern (such as the Beta and Mu variants in study VAC31518COV3001 and the Delta variant in the Sisonke study[a]) remains high against severe disease, hospitalization, and death, this protection is lower against, for example, the Gamma variant compared to the reference Wuhan strain. Protection against

[a]. Gray G, Bekker L-G. Sisonke Update on the Janssen®(JNJ) Ad26.COV2.S vaccine. https://sacoronavirus.co.za/wp-content/uploads/2021/08/Sisonke-Provisional-Results-6-August-2021GG2.pdf (accessed September 21, 2021).

severe/critical disease caused by different variants of concern (such as Gamma, Lambda and Mu variants) was shown to be reduced in the final analysis of study VAC31518COV3001 compared to the reference Wuhan strain and the Alpha variant, for example. Giving a second dose of Ad26.COV2.S results in marked increases of immune responses and those higher immune responses correlate with better protection against COVID-19, as shown in the primary analysis of study VAC31518COV3009[a]. Some national vaccination recommendation bodies (eg, CDC[b]) have recently advised to give a booster vaccination. Therefore, based on this recommendation for a booster vaccination and the availability of booster vaccinations outside the study, this amendment will permit boosting of all eligible participants in this study who have previously received 1 or more doses of any COVID-19 vaccine.

These and other changes made to the clinical protocol of study VAC31518COV1001 are listed below, including the rationale for each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.4 End of Study Definition 5 STUDY POPULATION 5.5 Criteria for Temporarily Delaying Administration of Study Vaccination 6.1 Study Vaccinations Administered 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine After the End of the Study 6.8 Prestudy and Concomitant Therapy 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.1 Immunogenicity Assessments 8.7 Assessments and Procedures for Ad Hoc Booster Vaccination	At the ad hoc booster vaccination visit, all eligible participants will be offered a single ad hoc booster dose of Ad26.COV2.S vaccine (5×10^{10} vp). The ad hoc booster vaccination will be provided to participants who have previously received 1 or more doses of any COVID-19 vaccine (ie, the Ad26.COV2.S vaccine, an mRNA vaccine and/or another COVID 19 vaccine authorized for primary vaccination including protein, inactivated, and adenovector-based vaccines) if the last vaccination was ≥6 months ago. Safety and immunogenicity follow-up visits are scheduled at 28 days, 6 months, and 12 months after ad hoc booster vaccination. Procedures and assessments for safety and immunogenicity follow-up phase for the ad hoc booster vaccination have been added. The study duration and study completion definition have been adapted accordingly. Blood volumes to be collected in the study for the ad hoc booster vaccination phase were added. Objectives & endpoints were added for the ad hoc booster vaccination phase of the study. Added that a dose level of 5×10^{10} vp in a volume of 0.5 mL will be administered to	See overall rationale for amendment.

[a] Johnson & Johnson News Release. Johnson & Johnson Announces Real-World Evidence and Phase 3 Data Confirming Strong and Long-Lasting Protection of Single-Shot COVID-19 Vaccine in the U.S. Press Release, New Brunswick, N.J., 21 September 2021. Available at: https://www.janssen.com/emea/sites/www janssen com emea/files/johnson johnson announces real-world evidence and phase 3 data confirming strong and long-lasting prote.pdf. Accessed on 28 September 2021.

[b] Centers for Disease Control and Prevention. CDC Statement on ACIP Booster Recommendations. Press Release 24 September, 2021. Available at: https://www.cdc.gov/media/releases/2021/p0924-booster-recommendations-.html. Accessed on: 30 September 2021.

Section Number and Name	Description of Change	Brief Rationale
9.6 Analyses for Participants Requesting Unblinding to Receive an Authorized/Licensed COVID-19 Vaccine 9.8 Analysis After Receipt of the Ad Hoc Booster Vaccination 10.2.2 Additional Hematology and Coagulation Testing 10.3.3 Informed Consent Process	participants that are eligible for and have consented to receive an ad hoc booster vaccination. Statistical considerations for the analysis of the ad hoc booster vaccination phase were added.	
1.1 Synopsis 4.1 Overall Design 8.1.2 Procedures in Case of COVID 19-like Signs and Symptoms	Following local approval of protocol Amendment 15, the participant will not be required to complete the daily calendar booklet but will be contacted by the site regularly to check whether they experienced COVID 19 like symptoms.	Update
1.1 Synopsis 1.3.10 Procedures for Participants Receiving an Ad Hoc Booster Vaccination of $5x10^{10}$ vp Ad26.COV2.S 2.3.1 Risks Related to Study Participation 5.2 Exclusion Criteria 8.3.5 Pregnancy 8.7 Assessments and Procedures after Protocol Amendment 15 Approval (Ad Hoc Booster Vaccination)	Participants who are pregnant may receive ad hoc booster vaccination with Ad26.COV2.S, if allowed by local regulations and if the investigator considers that the potential benefits outweigh the potential risks to the mother and fetus.	Update
2.3.1 Risks Related to Study Participation	Updated that Guillain-Barré syndrome (GBS) is considered an important identified risk for Ad26.COV2.S. It was added that no clinical data are available for Ad26.COV2.S administration after previous vaccination with a COVID-19 vaccine other than Ad26.COV2.S. Available clinical information on the administration of an Ad26.COV2.S booster vaccination following a single dose of Ad26.COV2.S was added.	To update the potential risks.
2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design 6.7 Treatment of Overdose 8.3.2 Method of Detecting Adverse Events, Adverse	Added that participants will remain under observation at the study site for at least 15 minutes to 1 hour depending on the vaccination being administered.	Participants who received placebo only during primary regimen and who accepted a single dose of 5×10^{10} vp Ad26.COV2.S after unblinding and participants that receive an ad hoc booster vaccination will remain under observation at the study site for at least 15 minutes.

Section Number and Name	Description of Change	Brief Rationale
Events of Special Interest, and Serious Adverse Events		
1.1 Synopsis 1.2 Schema 1.3.2 Cohort 1b 1.3.2.1 Optional Lymph Node Aspirates for Cohort 1b Participants (Beth Israel Deaconess Medical Center [BIDMC]) 1.3.7 Procedures for Group 5 (Placebo Only) Participants Receiving a Single Dose of $5x10^{10}$ vp Ad26.COV2.S (Placebo Crossover Vaccination) after EUA or Approval in any Country 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.1 Immunogenicity Assessments 8.1.1.1 Optional Lymph Node Aspiration 9.4.5 Other Analyses 10.1 Abbreviations 10.3.3 Informed Consent Process 10.4.1 Adverse Events and Classification 10.4.5 Procedures	Addition of optional fine needle lymph node aspirates (LNAs) for Cohort 1b at approximately 12 months after the second vaccination. In addition, details on the method, risks related to study participation, analysis, informed consent process, and adverse events, are added in the respective sections.	Additional analysis for Cohort 1b (site BIDMC only) to allow for further exploration of immune responses in lymph nodes to better understand the increase in neutralizing activities of the antibodies against variants, generated by Ad26.COV2.S.
1.3.8 Procedures for Participants with a Suspected AESI	It is clarified that also in the event of thrombocytopenia, laboratory assessments (to be performed locally) are required to facilitate diagnosis and determine treatment options, including but not limited to platelet count and anti-PF4 tests. It is clarified that all local laboratory results need to be encoded in the eCRF, including platelet counts. Low platelet counts are to be recorded as a suspected AESI (thrombocytopenia).	Clarification
10.2 Appendix 2: Clinical Laboratory Tests	For the clinical evaluation of suspected AESIs, added that it is upon discretion of the sponsor that all or some of the coagulation-related assays may be conducted on the stored pre-vaccination sample and on the AESI samples.	Clarification

Section Number and Name	Description of Change	Brief Rationale
	Added that, as part of investigation of any AESI, samples from appropriate controls (from vaccinated participants who did not experience an AESI) within the study could be used for coagulation-related assays.	
10.3.3 Informed Consent Process	Added that a new ICF needs to be signed for − Participants from Cohort 1a, 1b, and 3 who wish to participate in the additional follow-up. − Participants receiving a single ad hoc booster dose of $5x10^{10}$ vp Ad26.COV2.S after local approval of protocol amendment 15.	Update
1.1 Synopsis 11 REFERENCES	The reference to the Brighton Collaboration case definition of thrombotic events and thrombocytopenia was updated.	Update
Throughout the protocol	The term 'placebo crossover vaccination' was introduced to define the single vaccination with Ad26.COV2.S in the open-label phase that is offered to participants that were randomized to the placebo arm in the double-blind phase.	Clarification
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added throughout the protocol.	Correction of minor errors and inconsistencies. Addition of minor clarifications.

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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): PPD

Institution: Janssen Research & Development

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
PPD	18-Aug-2022 12:54:58 (GMT)	Document Approval