Janssen Vaccines & Prevention B.V.*

Clinical Protocol

Protocol Title

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels and Vaccination Intervals of Ad26.COV2.S in Healthy Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older and to Evaluate 2 Dose Levels of Ad26.COV2.S in Healthy Adolescents Aged 12 to 17 Years Inclusive

Protocol VAC31518COV2001; Phase 2a

AMENDMENT 6

VAC31518 (JNJ-78436735)

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	This document
Amendment 5	18 May 2021
Amendment 4	04 March 2021
Amendment 3	22 December2020
Amendment 2	29 October 2020
Amendment 1	21 August 2020
Original Protocol	23 July 2020

Amendment 6 (This document)

Overall Rationale for the Amendment: The purpose of the amendment is to cease recruitment of adolescents in this study.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) enrolled in the study in the 16-17 year old age group at a dose of $2.5x10^{10}$ vp enrolled in this study, the entire Ad26.COV2.S COVID-19 vaccine program was paused to evaluate a safety concern of thrombosis with thrombocytopenia (TTS) in adults. During this pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated (see current version of Investigator's Brochure[0]). While the Independent Data Monitoring Committee (IDMC) endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level, the sponsor made the decision not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose in Study VAC31518COV2001 and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12-17 years of age, and no further enrollment of this age group will take place in this study. The 33 adolescents already enrolled at the time of Amendment 6 will continue to be followed in this study in accordance with the planned Schedule of Activities, but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at 2.5 $x10^{10}$ vp.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.5 Groups A to C – Adolescents 1.3.6 Active Vaccine Regimen: Placebo Group C – Adolescents 2.1 Study Rationale 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.3 Justification for Dose 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Dose Modification 8. STUDY ASSESSMENTS AND PROCEDURES 9.2 Sample Size Determination 9.4.1 General Considerations	Text was modified to indicate that total enrollment for the adolescent groups will be 33 (11 sentinels and 22 participants in the safety cohort for the 16-17 year old age group). Text regarding enrollment of adolescent participants in Groups D-F, and the 2-dose regimen and booster for Groups A and B was deleted. Visit days were renumbered accordingly. Text was modified to indicate that participants in Group C who initially received placebo will receive a single dose of active Ad26.COV2.S vaccine at a dose level of $2.5x10^{10}$ vp, rather than a 2-dose regimen. All enrolled adolescent participants will be followed for 12 months post vaccination 1.	Due to the reactogenicity observed at the $2.5x10^{10}$ vp dose level, it was decided not to proceed to the $5x10^{10}$ vp dose level in adolescents. The immunogenicity in the 33 enrolled adolescents with $2.5x10^{10}$ vp was similar to that of young adults who received $5x10^{10}$ vp in other studies with Ad26.COV2.S, the sponsor has decided to cease enrollment of adolescents in these study and to study the safety, reactogenicity and immunogenicity of Ad26.COV2.S with a dose selection component under separate study protocols.
1.1 Synopsis 2.1 Study Rationale 3 OBJECTIVES AND ENDPOINTS 9.1 Statistical Hypotheses 9.2.1 Immunogenicity 9.4.2 Primary/Secondary Endpoints 9.5 Planned Analysis	Text was modified to indicate that no formal hypothesis testing will occur in this study. Non-inferiority testing of adolescents vs adults was removed from the study objectives. Text regarding the interim and primary analyses for adolescent participants was deleted.	The 33 participants (sentinels and Safety Cohort in the 16-17 year old age group) will be followed for safety and immunogenicity.. No non-inferiority statistical analysis with data from adult participants will be performed. Safety and immunogenicity data will be summarized for the 33 enrolled adolescent participants.
1.3.8 Participants with a Suspected AESI – Adults and Adolescents 8. STUDY ASSESSMENTS AND PROCEDURES	The total blood volume to be drawn at Day 1 and Day 29 of a suspected adverse event of special interest (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 a suspected AESI.
1.3.5 Groups A to C – Adolescents 1.3.6 Active Vaccine Regimen: Placebo Group C – Adolescents 8. STUDY ASSESSMENTS AND PROCEDURES	Total blood volumes to be drawn in adolescents were updated after vaccination 2 and booster-related assessments were deleted. The 6-months post-vaccination 1 visit was changed from a safety phone call to an on-site safety and immunogenicity visit.	Corresponding updates
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.2.4 Hematology Clinical Laboratory Assessments	Anti-PF4 was added as an exploratory endpoint for adolescent participants.	This was added to more fully evaluate coagulation parameters.

Section Number and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Hematology Clinical Laboratory Tests		
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Adenovirus neutralization as measured by VNA was added as an exploratory endpoint for adults and adolescents.	To align with other study protocols
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 1.3.5 Groups A to C – Adolescents 1.3.6 Active Vaccine Regimen: Placebo Group C – Adolescents 8. STUDY ASSESSMENTS AND PROCEDURES 8.1.1 Immunogenicity Assessments	Text related to assessment of cellular immunogenicity (PBMC) in adolescents was removed.	Per existing protocol text, adolescent participants who were sentinels or in the safety cohorts were not to be included in the PBMC subset. Therefore, none of the 33 enrolled adolescents have had or will have these blood draws.
9.5 Planned Analysis	Text was modified to indicate that participants, clinical staff, and study-site personnel will remain blinded to the study vaccine allocation until the implementation of protocol Amendment 5 (adults) or Amendment 6 (adolescents).	Alignment with other protocol sections
1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 8 STUDY ASSESSMENTS AND PROCEDURES	Hematology blood sample, plasma, 5 mL, was deleted from Groups 1-6 study visit 11 and 12, Groups 7-8 study visit 9 and 10, Groups 9-10 study visit 10 and 11. Total blood to be drawn (approximate per day and approximate cumulative total) was updated accordingly.	All adult participants received Injection 3 prior to implementation of protocol Amendment 4, so these draws were not collected from any participants.
7.1 Discontinuation of Study Vaccination	Text was added that participants who have a history of capillary leak syndrome or experienced this event after the first study vaccination should not be given further study vaccine.	Based on emerging post-marketing safety data
Throughout the protocol	Footnote was modified to reflect that adolescent sections of this protocol are not applicable to sites in the Netherlands and Germany. Minor grammatical, formatting, or spelling changes were made.	Clarification Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels and Vaccination Intervals of Ad26.COV2.S in Healthy Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older and to Evaluate 2 Dose Levels of Ad26.COV2.S in Healthy Adolescents Aged 12 to 17 Years Inclusive.

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) spike (S) protein, which will be assessed in this study.

OBJECTIVES AND ENDPOINTS

ADULTS

Objectives	Endpoints
Primary	
• To assess the humoral immune response to 3 dose levels ($5x10^{10}$ virus particle (vp), $2.5x10^{10}$ vp, $1.25x10^{10}$ vp) of Ad26.COV2.S, administered intramuscularly (IM) as a 2-dose schedule at a 56-day interval, 28 days after Vaccination 2.	• Serological response to vaccination as measured by virus neutralization assay (VNA) titers and enzyme-linked immunosorbent assay (S-ELISA, ELISA Units/mL [EU/mL]), 28 days after Vaccination 2. • Antibody geometric mean titers (GMTs) (VNA) and geometric mean concentrations (GMCs) (S-ELISA), 28 days after Vaccination 2.
• To assess the humoral immune response to 2 dose levels ($1 x10^{11}$ vp and $5x10^{10}$ vp) of Ad26.COV2.S, administered IM as a single vaccination, 28 days after Vaccination 1.	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 28 days after Vaccination 1. • Antibody GMTs (VNA) and GMCs (S-ELISA), 28 days after Vaccination 1.
• To assess the humoral immune response to Ad26.COV2.S at the $5x10^{10}$ vp dose level, administered IM as a 2-dose schedule at a 28-day and at an 84-day interval, 28 days after Vaccination 2.	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 28 days after Vaccination 2. • Antibody GMTs (VNA) and GMCs (S-ELISA), 28 days after Vaccination 2.
• To assess the safety and reactogenicity of Ad26.COV2.S, administered IM at several dose levels, as a 2-dose or a single-dose schedule.	• Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • Unsolicited AEs for 28 days after each vaccination. • Serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study (from first vaccination until end of the study).

Objectives	Endpoints
Secondary	
• To assess the anamnestic response to antigen presentation of Ad26.COV2.S at the $1.25x10^{10}$ vp dose level, administered 4 months after Vaccination 2 (2-dose schedule) or 6 months after a Vaccination 1 (single-dose schedule), 7 days after antigen presentation (Groups 1-5, 7 and 9).	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 7 days after antigen presentation. • Antibody GMTs (VNA) and GMCs (S-ELISA), 7 days after antigen presentation.
• To assess the safety and reactogenicity of antigen presentation of Ad26.COV2.S at the $1.25x10^{10}$ vp dose level, administered 4 months after Vaccination 2 (2-dose schedule) or 6 months after a Vaccination 1 (single-dose schedule) (Groups 1-5, 7 and 9).	• Solicited local and systemic AEs for 7 days after antigen presentation. • Unsolicited AEs for 28 days after antigen presentation. • SAEs and AESIs throughout the study (from antigen presentation until end of the study).
• To assess the humoral immune response to Ad26.COV2.S across all groups, at all blood collection timepoints.	• Neutralizing antibody titers to the wild-type SARS-CoV-2 virus expressing S protein as measured by VNA, at all blood collection timepoints. • Binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA, at all blood collection timepoints.
Exploratory	
• To assess the cellular immune response to Ad26.COV2.S at different dose levels in a subset of participants (Groups 1 to 6) at selected blood collection timepoints.	• 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 (PBMC) and intracellular staining (ICS) including cluster of differentiation (CD) 4^+/$CD8^+$, interferon gamma (IFNγ), interleukin (IL)-2, tumor necrosis factor alpha (TNFα), IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.
• To further assess the humoral immune response to Ad26.COV2.S.	• 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). • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype. • Passive transfer: analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model.

Objectives	Endpoints
	• Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants. • Adenovirus neutralization as measured by VNA.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms.	• The number of participants with molecularly confirmed COVID-19. • Presence and severity of COVID-19 signs and symptoms as measured by Symptoms of Infection with Coronavirus-19 (SIC).
• To examine the immune response in vaccinated individuals after natural SARS-CoV-2 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 pseudovirions expressing S protein). • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein. • Analysis of gene expression by ribonucleic acid (RNA) transcript profiling.
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of asymptomatic participants with positive non-S protein ELISA (eg, nucleocapsid [N] protein ELISA), as feasible. • The number of asymptomatic participants with a SARS-CoV-2 positive RT-PCR test.
• To assess hematology laboratory parameters after Ad26.COV2.S administration.	• Lupus anticoagulants, anti-β2 glycoprotein, anti-cardiolipin, D-dimers; anti-PF4.
• To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints.

ADOLESCENTS[a]

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of a single dose of Ad26.COV2.S, administered IM at the $2.5x10^{10}$vp dose level.	• Solicited local and systemic AEs for 7 days after vaccination. • Unsolicited AEs for 28 days after vaccination.

[a] Not applicable in Germany and the Netherlands

Objectives	Endpoints
	• SAEs (incl. Multisystem Inflammatory Syndrome in Children [MIS-C]) and AESIs throughout the study (from first vaccination until end of the study).
Secondary	
• To assess the humoral immune response to a single dose of Ad26.COV2.S at the $2.5x10^{10}$ vp dose level, administered IM.	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 28 days after vaccination. • Antibody GMTs (VNA) and GMCs (S-ELISA), 28 days after vaccination.
• To assess the humoral immune response to Ad26.COV2.S at the $2.5x10^{10}$ vp dose level, at all blood collection timepoints.	• Neutralizing antibody titers to the wild-type SARS-CoV-2 virus expressing S protein as measured by VNA, at all blood collection timepoints. • Binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA, at all blood collection timepoints.
Exploratory	
• To further assess the humoral immune response to Ad26.COV2.S.	• 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). • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype. • Passive transfer: analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. • Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants. • Adenovirus neutralization as measured by VNA.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms.	• The number of participants with molecularly confirmed COVID-19. • Presence and severity of COVID-19 signs and symptoms as measured by Symptoms of Infection with Coronavirus-19 (SIC).
• To examine the immune response in vaccinated individuals after natural SARS-CoV-2 infection and to explore other	• Confirmation of SARS-CoV-2 infection by molecular testing.

Objectives	Endpoints
potentially informative biomarkers (eg, those associated with more severe disease).	• SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirions expressing S protein). • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein. • Analysis of gene expression by ribonucleic acid (RNA) transcript profiling.
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of asymptomatic participants with positive non-S protein ELISA (eg, nucleocapsid [N] protein ELISA), as feasible. • The number of asymptomatic participants with a SARS-CoV-2 positive RT-PCR test.
• To assess coagulation-related parameters at selected blood sample collection timepoints.	• platelet factor 4-heparin complex (anti-PF4) antibodies.

HYPOTHESIS

No formal hypothesis testing will be performed in this study.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adolescents aged 12 to 17 years inclusive, adults aged 18 to 55 years inclusive and adults in good or stable health aged 65 years and older. Countries may participate in the adult and adolescent portions of the study or they may participate in either the adult or adolescent portion.

In adults, the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in 1- and 2-dose vaccination regimens followed by antigen presentation after 4 months (2-dose regimen) or 6 months (single-dose regimen), will be evaluated across a range of dose levels and vaccination intervals.

In adolescents, the safety, reactogenicity, and immunogenicity of a single dose of Ad26.COV2.S will be evaluated.

Participants will receive Ad26.COV2.S or a placebo. In adults, 4 dose levels of Ad26.COV2.S will be administered IM: $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp. Adolescents will be administered $2.5x10^{10}$ vp.

ADULTS

A target of approximately 550 adult participants will initially be enrolled in this study in a blinded manner and randomly assigned to 1 of 10 groups to receive 1- or 2-doses of active Ad26.COV2.S vaccine or placebo at a dose of $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp, or $1.25x10^{10}$ vp and at a 28-day, 56-day or 84-day interval.

A single antigen presentation injection with $1.25x10^{10}$ vp Ad26.COV2.S (Groups 1-5, 7, 9) will be administered 4 months after the second vaccination (ie, 4 months post vaccination 2 in the 2-dose regimens and 6 months after Vaccination 1 in the 1-dose regimens) to all participants who received active vaccine in the primary vaccine regimen.

After each vaccination, all participants will remain under observation at the study site for at least 1 hour to monitor for the presence of any acute reactions and solicited events.

Participants who were initially enrolled to receive placebo (Groups 6, 8 and 10), will be offered a 2-dose (28-day interval) Ad26.COV2.S vaccination regimen at the $5x10^{10}$ vp dose level. In October 2020, the study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2 (Visit 4), rendering the intent of the 28-day vaccination interval in these groups futile. The goal in offering 2 doses of study vaccine to those participants who initially received placebo in this study is to recreate this 28-day vaccination interval, and to restore the objectives associated with this interval. The original 28-day interval target group was 75 participants. Hence the total number of placebo recipients from Groups 6, 8 and 10 (target n=75) is intended to fulfill the original target enrollment for Group 7.

With the implementation of Amendment 5, all adult participants will be unblinded to the primary vaccination regimen, and adults who received placebo in the primary vaccine regimen will receive a 2-dose active Ad26.COV2.S vaccine regimen at a 28-day interval and at a dose level of $5x10^{10}$ vp, in an open-label manner. Per group, approximately one third of participants will be 65 years and older.

Adult participants who received the active vaccine in the primary vaccine regimen will be followed up for 12 months after vaccination 2; adult participants who received placebo in the primary vaccine regimen will be followed up for 6 months after receipt of the unblinded vaccination 1 (ie, receipt of the first active vaccine following unblinding).

Groups 1-6

400 participants (75 participants per active vaccine group, 25 in the placebo group) will be randomized in parallel in a 3:3:3:3:3:1 ratio to 1 of 6 vaccination groups. Participants will receive a 2-dose (56-day interval, Groups 1-3) vaccination regimen at different dose levels (5×10^{10} vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) or single-dose vaccination regimen (Groups 4-5) at different dose levels (1×10^{11} vp, $5x10^{10}$ vp), or placebo (Group 6). For blinding purposes, participants in the single-dose groups (Groups 4-5) will receive a placebo vaccination on Day 57. Additional exploratory cellular immunogenicity evaluations (PBMC) will be performed in a subset of participants (21/group in Groups 1-5, 7 in Group 6; at selected sites). Participants in Group 6 who received 2-doses of placebo in the primary vaccine regimen will receive 2 doses of active vaccine at a single dose level of $5x10^{10}$ vp, at a 28-day interval.

Groups 7-8

75 participants (50 participants in the active vaccine group, 25 in the placebo group) will be randomized in parallel in a 2:1 ratio, to 1 of 2 vaccination groups. Participants will receive a 2 dose (28-day interval, Groups 7) vaccination regimen at a 5×10^{10} vp dose level or placebo (Group 8). Participants in Group 8 who received 2-doses of placebo in the primary vaccine regimen will receive 2 doses of active vaccine at a single dose level of $5x10^{10}$ vp, at a 28-day interval.

Groups 9-10

75 participants (50 participants in the active vaccine group, 25 in the placebo group) will be randomized in parallel in a 2:1 ratio, to 1 of 2 vaccination groups. Participants will receive a 2 dose (84-day interval, Group 9) vaccination regimen at a 5×10^{10} vp dose level or placebo (Group 10). Participants in Group 10 who received 2-doses of placebo in the primary vaccine regimen will receive 2 doses of active vaccine at a single dose level of $5x10^{10}$ vp, at a 28-day interval.

Vaccination Schedule – Adults

Adults ≥18 to ≤55 Years and ≥65 Years

Group	N	Day 1 (Vaccination 1) Ad26.COV2.S dose level / placebo	Day 29 (Vaccination 2) Ad26.COV2.S dose level / placebo	Day 57 (Vaccination 2) Ad26.COV2.S dose level / placebo	Day 85 (Vaccination 2) Ad26.COV2.S dose level / placebo	4 Months Post Vaccination 2 (Injection 3)[1] Ad26.COV2.S dose level/ placebo	Unblinded Vaccination 1 Ad26.COV2.S dose level	Day 29 Post Unblinded Vaccination 1 (Unblinded Vaccination 2) Ad26.COV2.S dose level
1	75	**5**x10^{10} vp		**5**x10^{10} vp		**1.25**x10^{10} vp	-	-
2	75	**2.5**x10^{10} vp		**2.5**x10^{10} vp		**1.25**x10^{10} vp	-	-
3	75	**1.25**x10^{10} vp		**1.25**x10^{10} vp		**1.25**x10^{10} vp	-	-
4	75	**1**x10^{11} vp		Placebo		**1.25**x10^{10} vp[2]	-	-
5	75	**5**x10^{10} vp		Placebo		**1.25**x10^{10} vp[2]	-	-
6	25	Placebo		Placebo		Placebo	**5**x10^{10} vp	**5**x10^{10} vp
7	50	**5**x10^{10} vp	**5**x10^{10} vp			**1.25**x10^{10} vp	-	-
8	25	Placebo	Placebo			Placebo	**5**x10^{10} vp	**5**x10^{10} vp
9	50	**5**x10^{10} vp			**5**x10^{10} vp	**1.25**x10^{10} vp	-	-
10	25	Placebo			Placebo	Placebo	**5**x10^{10} vp	**5**x10^{10} vp

N number of participants; vp virus particles.

1. Antigen presentation
2. 6 Months after Vaccination 1 in the single dose regimens (Groups 4 and 5).

ADOLESCENTS[a]

From the time of protocol Amendment 2, adolescent participants (12 to 17 years of age, inclusive) were to be enrolled in a randomized and staggered manner.

The safety profile of Ad26.COV2.S in adolescents was planned to be assessed separately by age group and by escalating dose, with the 2 adolescent age groups (12 to 15 years and 16 to 17 years) assessed independently and enrollment progressing in a sequential manner. The safety and tolerability of the Ad26.COV2.S vaccine was to be assessed in the first instance in a group of sentinels at Day 4 post-vaccination, and if acceptable, in the larger safety cohort at Day 8 post-vaccination. The Day 4 and Day 8 post-vaccination safety profiles of the Ad26.COV2.S vaccine at the $2.5x10^{10}$ vp dose level in the sentinel and safety cohorts was to be assessed in participants at 16 to 17 years of age, by the Safety Monitoring Committee (SMC) before progressing to enrollment of the sentinel group of participants at 12 to 15 years of age.

The first doses of Ad26.COV2.S study vaccine at $2.5x10^{10}$ vp were to be administered to a sentinel group of 11 participants in Groups A-C (randomly assigned at a ratio of 5:5:1 to Ad26.COV2.S, with 5 each from Groups A and B, and 1 participant in Group C to receive placebo), to monitor for any unexpected severe adverse reactions. The sentinel participants were to be vaccinated at least 1 hour apart even if enrolled at different study sites. A telephone call was to be made to each of these 11 sentinel participants on Day 4 post-vaccination to collect safety data, which was to include solicited and unsolicited AEs and SAEs. The collected data were to be reviewed in a blinded manner by the principal investigator and the sponsor's study responsible physician/scientist (SRP/S). Randomization and vaccination of additional participants was to be halted until the review was completed. The SMC was to review the unblinded Day 4 post-vaccination safety data, including solicited and unsolicited AEs and SAEs, and if the safety profile was found to be acceptable, a safety cohort of 22 participants in Groups A-C (randomly assigned at a ratio of 5:5:1 to Ad26.COV2.S, with 10 each from Groups A and B, and 2 participants in Group C to receive placebo) was to be enrolled. The Day 8 post-vaccination safety data from both sentinel groups, including solicited and unsolicited AEs and SAEs, was also to be reviewed by the SMC, and in the absence of any safety concerns, the enrollment and vaccination of the remainder of the participants for Groups A-C (49 participants) in this age group was to proceed, and simultaneously, sentinel enrollment in Groups D-F (to receive Ad26.COV2.S study vaccine at $5x10^{10}$ vp) was to start. In addition, enrollment of the younger age group of adolescents (12-15 years, inclusive) was to proceed for Groups A-C.

After vaccination, all participants were to remain under observation at the study site for at least 1 hour (including participants in the Sentinel and Safety Cohort) to monitor for the presence of any acute reactions and solicited events.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16-17 year old age group at a dose of $2.5x10^{10}$ vp enrolled in this study, the entire Ad26.COV2.S COVID-19 vaccine program was paused to evaluate the a safety concern of thrombosis with thrombocytopenia (TTS) in adults. During this pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated (see current version of Investigator's Brochure[0]). While the IDMC endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level, the sponsor has decided not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose in Study VAC31518COV2001 and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12-17 years of age, and no further enrollment of this age group will take place in this study.

[a] Not applicable in Germany and the Netherlands

Therefore, per protocol Amendment 6, the 33 adolescents already enrolled will continue to be followed in this study in accordance with the planned Schedule of Activities (Sections 1.3.5 and 1.3.6), but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at 2.5 x10^{10} vp.

With the implementation of Amendment 6, the 33 adolescent participants will be unblinded to the primary vaccination regimen. Participants who were initially randomized to receive placebo (Group C), will receive a single dose of Ad26.COV2.S at the 2.5 x10^{10} vp dose level in an open-label manner.

Vaccination Schedules – Adolescents

Adolescents: 12 to 17 Years of Age, Inclusive

Group	Day 1 (Vaccination 1) Ad26.COV2.S dose level/placebo	Implementation of Amendment 6 (At approximately 6 Months of Study Participation) (Unblinded Vaccination 1) Ad26.COV2.S dose level
A	**2.5**x10^{10} vp	-
B	**2.5**x10^{10} vp	-
C	Placebo	**2.5**x10^{10} vp

vp virus particles.

ADULTS AND ADOLESCENTS

Initially, an internal Data Review Committee (DRC) was commissioned for this study. However, an IDMC was installed for the different studies throughout the COVID-19 vaccine program. The charter was updated to include VAC31518COV2001 on 29 October 2020, and the IDMC kickoff for review was held on 15 December 2020, after which the IDMC took over the responsibilities of the DRC in this study.

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms, and for documentation of body temperature and pulse oximetry results. Baseline pulse oximetry will be conducted at Visit 1. If participants meet one of the prespecified criteria for (suspected) COVID-19[a], the following should take place:

- Participants should contact the study site at the time of symptom onset/at time of becoming aware of the positive RT-PCR test.
- If the trigger was a sign or symptom: a nasal swab should be collected by 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. It is preferred that the swab is taken by a caregiver (spouse, partner, relative, friend, or health care professional). If that is not possible, the participant can collect the swab himself or herself. The site should arrange transfer of the sample to the study site as soon as possible after sample collection. If the trigger was a positive RT-PCR test, then this first nasal swab is not needed.
- A second nasal swab will be obtained on COVID-19 Day 3-8 following the same procedures as the first nasal swab. The second nasal swab may also be collected at home, at the hospital, or at another location, if needed, by a study site staff, if appropriate procedures are in place. The presence of SARS-CoV-2 infection will be assessed at the study site by molecular testing using the nasal swab samples. The nasal swabs may be tested at the central laboratory for the presence of SARS-CoV-2 and other respiratory pathogens using a broad respiratory pathogens panel. A physical examination, vital signs

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

measurements and pulse oximetry will be performed and a blood sample for assessment of the humoral immune response and other biomarkers will be taken. The sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

- From COVID-19 Day 3-8 onwards: Once a first negative swab is obtained, a second swab should be taken as soon as possible, but with a minimum of 1 day between the 2 swabs. This should be repeated until 2 consecutive negative swabs are obtained. These precautionary measures are to ensure that site staff who come into physical contact with a participant deemed to be a COVID-19 case undertake the proper safety procedures such as wearing of personal protective equipment.
- Participants should complete the SIC and record their highest body temperature daily starting on the first day of trigger onset. Blood oxygen saturation and pulse rate should be measured using a pulse oximeter 3 times a day, preferably in the morning, at lunch time, and in the evening.
- Collection of data will continue until resolution of the COVID-19 episode, defined as having 2 consecutive days with no COVID-19-related signs or symptoms and 2 consecutive SARS-CoV-2 negative nasal swabs.
- For participants with a positive test result for SARS-CoV-2 infection, a study visit will be conducted 28 days after trigger onset to assess the clinical course of the infection, record concomitant medications since trigger onset, and obtain a blood sample for assessment of the humoral immune response and other biomarkers.

The occurrence of asymptomatic SARS-CoV-2 infection will also be assessed, if feasible.

End of Study Definition

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

NUMBER OF PARTICIPANTS

Overall, a target of 550 adult participants aged 18 to 55 years, inclusive, and 65 years and older, and 33 adolescent participants, aged 12 to 17 years, inclusive, will be enrolled in this study.

DOSAGE AND ADMINISTRATION

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

- Ad26.COV2.S will be supplied at a concentration of $1x10^{11}$ vp/mL and $2x10^{11}$ vp/mL, as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer will be supplied as diluent. Dose levels throughout the different groups will be $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp and $1.25x10^{10}$ vp.
- Placebo will be supplied as a 0.9% NaCl solution.

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

IMMUNOGENICITY EVALUATIONS

Venous blood samples will be collected for assessment of humoral immune responses and cellular immunogenicity (RNA sequencing) in all participants. Blood for evaluation of humoral and cellular (PBMC in subset only) immune responses will be drawn from adult participants at the time points specified in the Schedule of Activities. Cellular immune responses (PBMC) will only be assessed in a subset of adult participants in Groups 1-6 (approximately 112; 21 participants per group in Groups 1-5, 7 participants in Group 6; at selected sites).Immunogenicity assessments may include, but are not limited to, the humoral and cellular immunogenicity assays (as available and feasible) summarized in the below table.

Table: Summary of Humoral and Cellular Immunogenicity Assays

Assay	Purpose
Humoral Immunogenicity	
Primary/Secondary/Exploratory endpoints	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein)
Exploratory endpoints	
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein, if such an assay is available
SARS-CoV-2 binding antibodies (MSD)	Analysis of antibodies binding to the SARS-CoV-2 S protein (different than the assays supportive of the secondary objectives) and the RBD of the SARS-CoV-2 S protein
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
SARS-CoV-2 neutralizing antibodies	Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants
Adenovirus neutralization (neutralization assays)	Analysis of neutralizing antibodies to adenovirus
Cellular Immunogenicity	
Exploratory endpoint	
Flow cytometry (ICS)	Analysis of T-cell responses to SARS-CoV-2 S protein, and/or other protein peptides by intracellular cytokine staining (ICS) including $CD4^+/CD8^+$, IFNγ, IL-2, TNFα, IL-4, IL-5, IL-13, and/or other Th1/Th2 markers
Gene expression analysis	Analysis of gene expression by RNA transcript profiling

CD = cluster of differentiation; ELISA = enzyme-linked immunosorbent assay; IFNγ = interferon gamma; IL = interleukin; MSD = meso scale discovery; PBMC = peripheral blood mononuclear cell; RBD = receptor-binding domain; RNA = ribonucleic acid; S = Spike protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; Th = T helper; TNFα = tumor necrosis factor alpha; VNA = virus neutralization assay

BIOMARKER EVALUATIONS

For participants with a positive test result for SARS-CoV-2 infection, blood will be drawn for evaluation of biomarkers (eg, those associated with severe COVID-19), 28 days after symptom onset.

SAFETY EVALUATIONS

After each vaccination, participants will remain under observation at the study site for at least 1 hour to monitor for the presence of any acute reactions and solicited events. Participants will be asked to note in the diary occurrences of injection site pain/tenderness, erythema and swelling at the study vaccine injection site daily for 7 days post vaccination (day of vaccination and the subsequent 7 days).

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. Participants will also be instructed on how to note signs and symptoms in the diary, on a daily basis, for 7 days post vaccination (day of vaccination and the subsequent 7 days), for the following events: fatigue, headache, nausea, and myalgia.

- AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated 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 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.
- From the time of local approval of protocol Amendment 5 onwards, TTS is considered to be an AESI. Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/μL[a]]) will be reported from the moment of vaccination until the end of the study/early withdrawal for adjudication. 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 adult participants chosen for this study will provide a preliminary safety and immunogenicity assessment. The number of adolescent participants has been chosen to provide sufficient power for the non-inferiority comparisons versus the adult population.

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 25, 50, 75 and 150 participants are vaccinated, the observation of 0 events (eg, SAEs) is associated with 95% confidence that the true event rate is below 11.3%, 5.8%, 3.9% and 2.0%, respectively, for the considered number of participants.

Sample size for the adolescent participants was originally calculated based on assessment of non-inferiority of immune responses with adults; however, following enrollment of the first 33 participants, further enrollment of adolescents will cease with this Protocol Amendment 6. (Refer to Overall Design - Adolescents for further details.)

Populations for Analysis Set

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[b]: The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural SARS-CoV-2 infection occurring after screening (if applicable) will be excluded from the analysis set.

[a] Reference for definition of thrombocytopenia: Brighton Collaboration. Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome (TTS). 21 April 2021. https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/. Accessed: 29 April 2021.

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

Primary/Secondary Endpoints

Immunogenicity

Descriptive statistics (geometric mean and confidence intervals, or median and interquartile range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters. Several definitions of serological response will be applied (fold increases in GMT [VNA] or GMC [ELISA]). 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 together with confidence intervals.

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

For adults, all data will be analyzed separately from the point of unblinding for safety and immunogenicity. Details will be described in the Statistical Analysis Plan (SAP).

For adolescents, limited pooled safety and reactogenicity data (planned for IDMC review) and group unblinded immunogenicity data (summary of S-ELISA, including GMC, and seroresponse rates for all participants and seronegative at baseline participants, in Ad26.COV2.S $2.5x10^{10}$ vp only) were reviewed by the sponsor prior to Amendment 6 (see Overall Design).

Safety

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 done on the FAS.

Planned Analyses

Interim and Primary Analyses for Adult Participants

An interim analysis of safety and immunogenicity will be performed, including all available immunogenicity data up to Day 29 (if applicable) and all available safety data post vaccination 1 of all groups in the adult cohort. Unblinded data at the vaccination group level will be available to the sponsor and might be used for regulatory submissions.

The primary analysis of safety and immunogenicity post-vaccination 2 will be performed when all adult participants have completed the visit that takes place 28 days after the second study vaccination in all groups or discontinued earlier. The analysis will include safety and immunogenicity data (VNA and ELISA) for all participants through Day 85 (Groups 1-6), Day 57 (Groups 7-8) or Day 113 (Groups 9-10). It will also include Th1-Th2 responses assessed only in Groups 1-6 (as available and feasible) through Day 85 (ie, 28 days after the second study vaccination). Unblinded data at the vaccination group level will be available to the sponsor and might be used for regulatory submissions.

A second interim analysis of safety and immunogenicity will be performed, including 28-day immunogenicity and 28-day safety data post antigen presentation (Groups 1-5, 7 and 9).

The final analysis of the adult cohort will be performed when all included adult participants have completed the last visit, or discontinued earlier.

Additional interim analyses may be performed for safety and/or immunogenicity to facilitate decision making with regards to the planning of future studies.

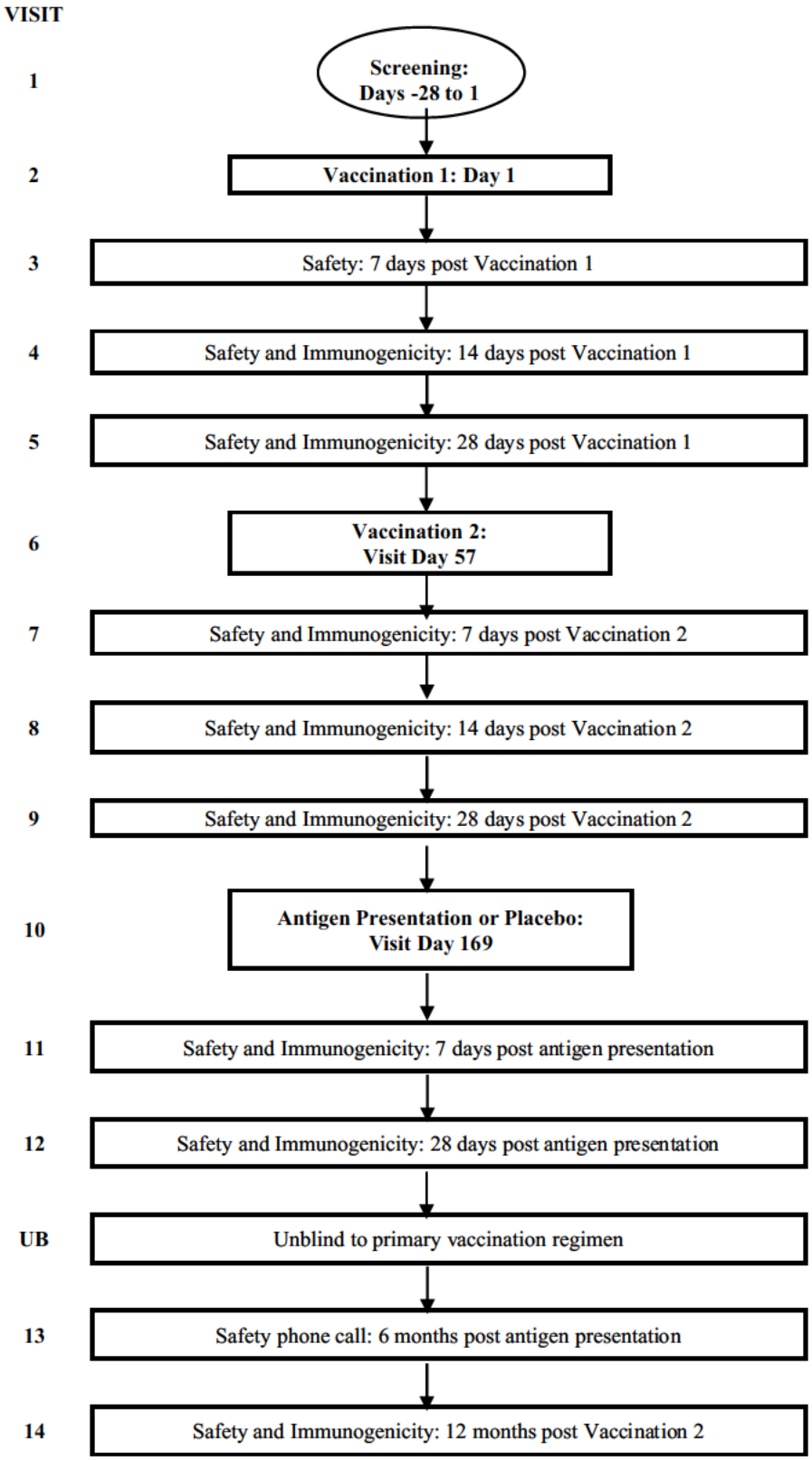
Unblinding due to availability of an authorized/licensed COVID-19 vaccine

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

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving 2 different COVID-19 vaccines. Participants who were already unblinded for any reason may receive Ad26.COV2.S vaccine upon discussion with the investigator, provided that they did not receive another COVID-19 vaccine. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the Schedule of Activities to the extent that the participant is amenable. All data will be analyzed separately from the point of unblinding, for safety and immunogenicity analysis, as described in the SAP.

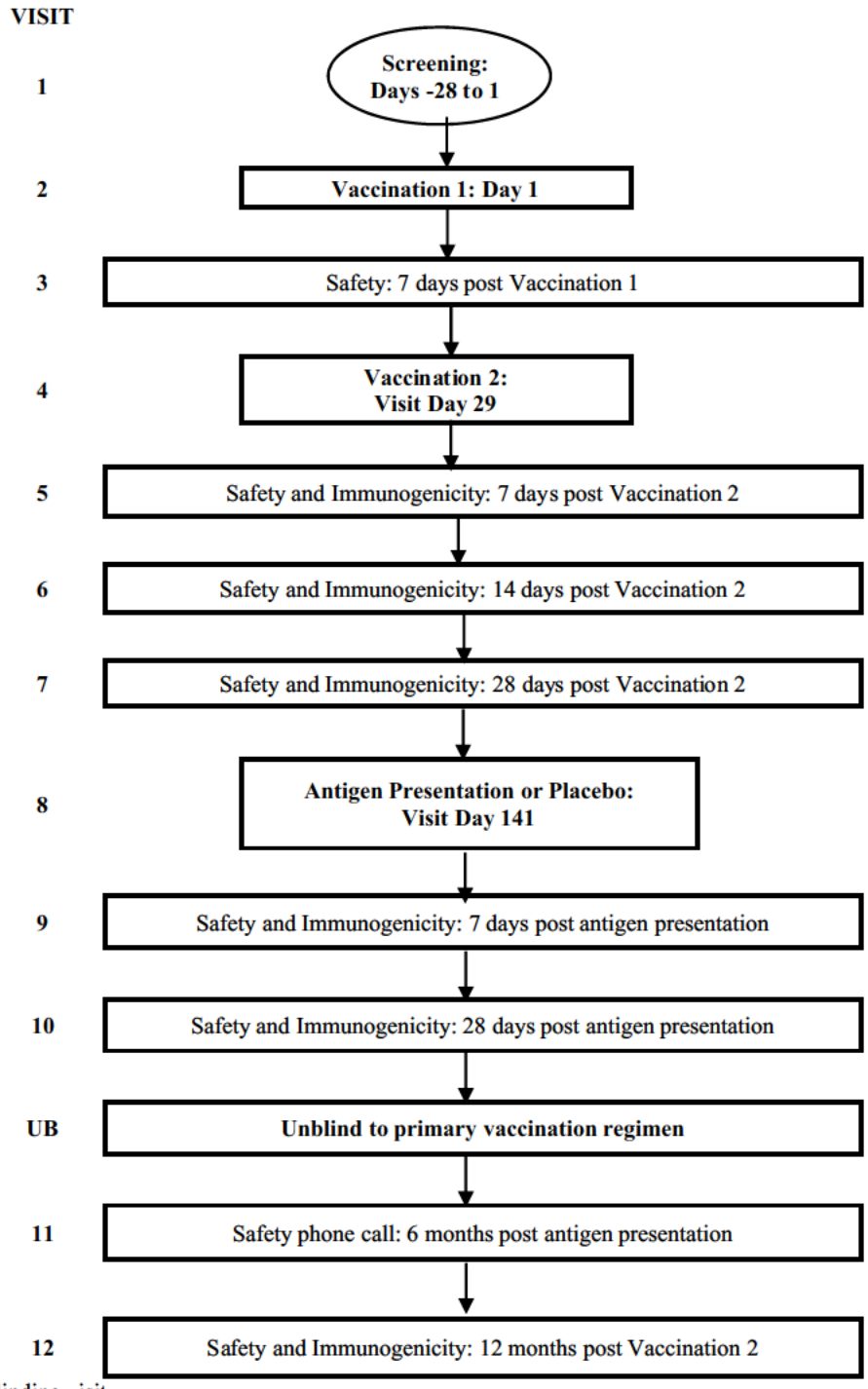
1.2. Schema

Figure 1: Schematic Overview of Groups 1-6 – Adults



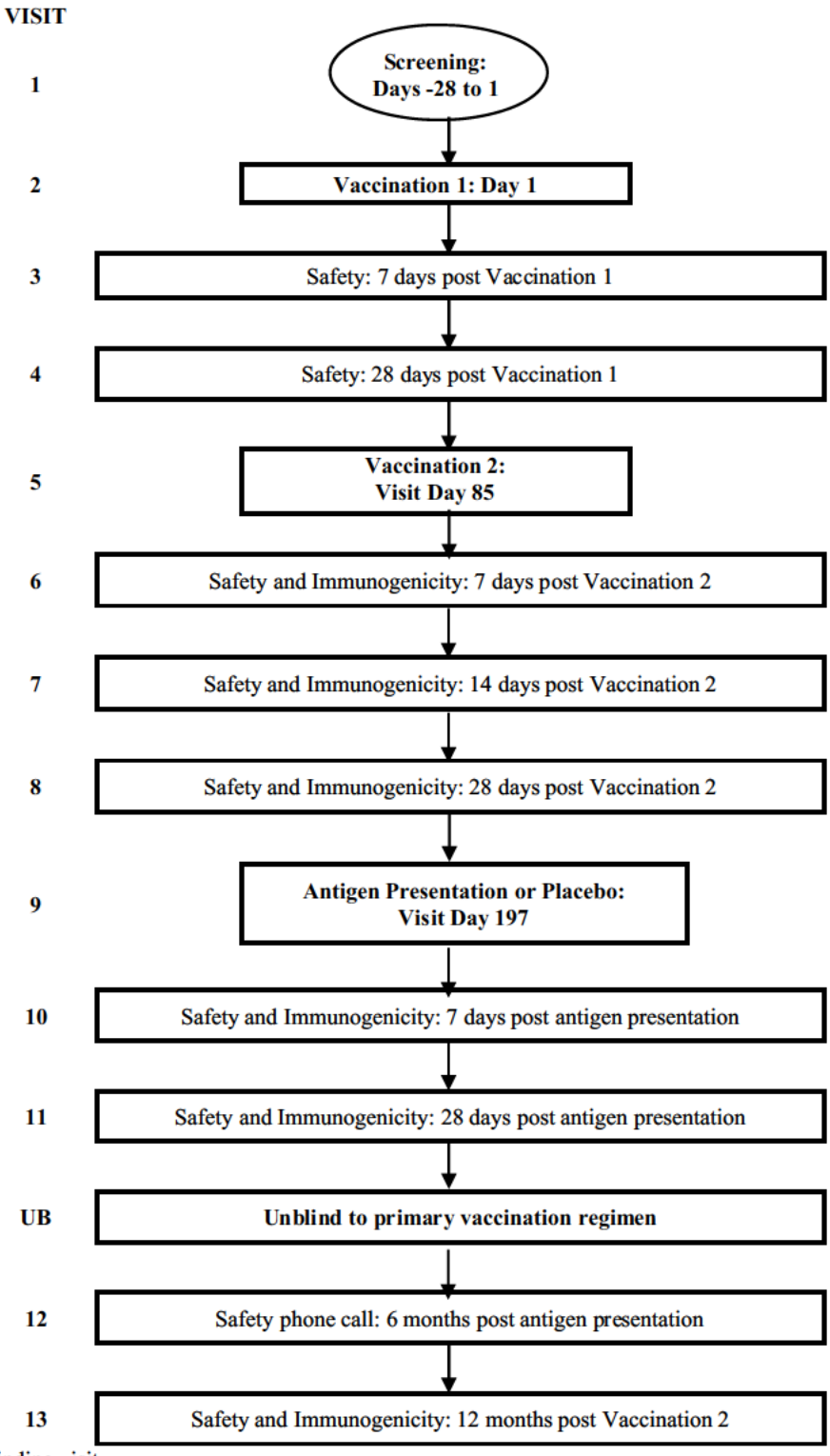
UB unblinding visit

Figure 2: Schematic Overview of Groups 7-8 – Adults



UB unblinding visit

Figure 3: Schematic Overview of Groups 9-10 -Adults



UB unblinding visit

Figure 4: Schematic Overview of Active Vaccine Regimen for Adult Placebo Groups 6, 8 and 10

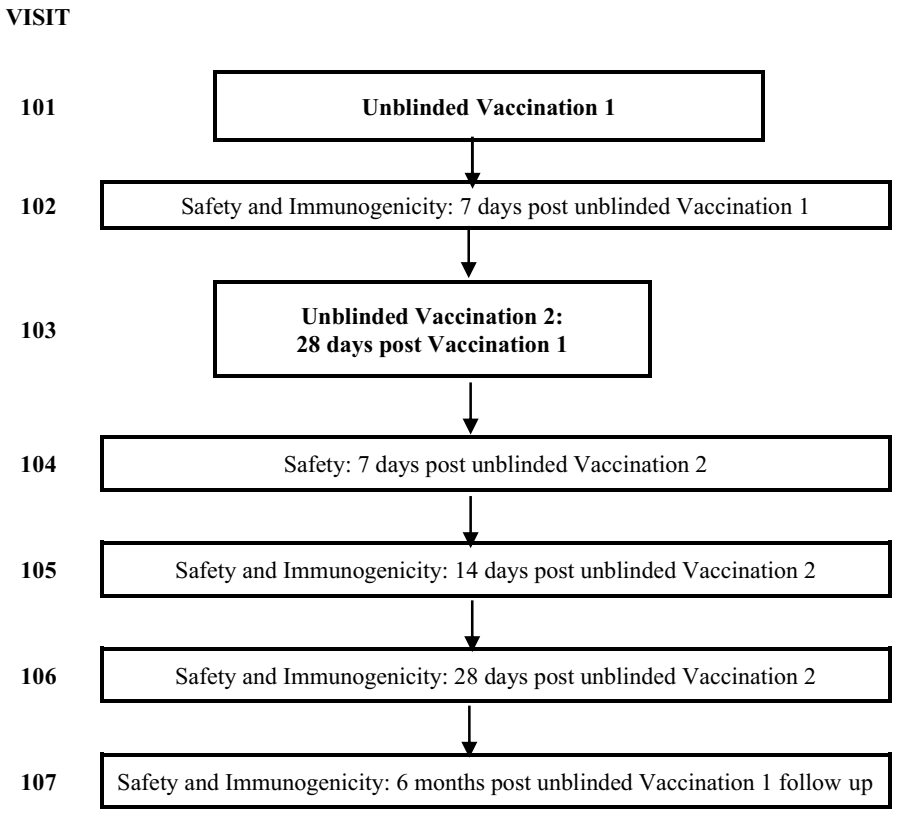
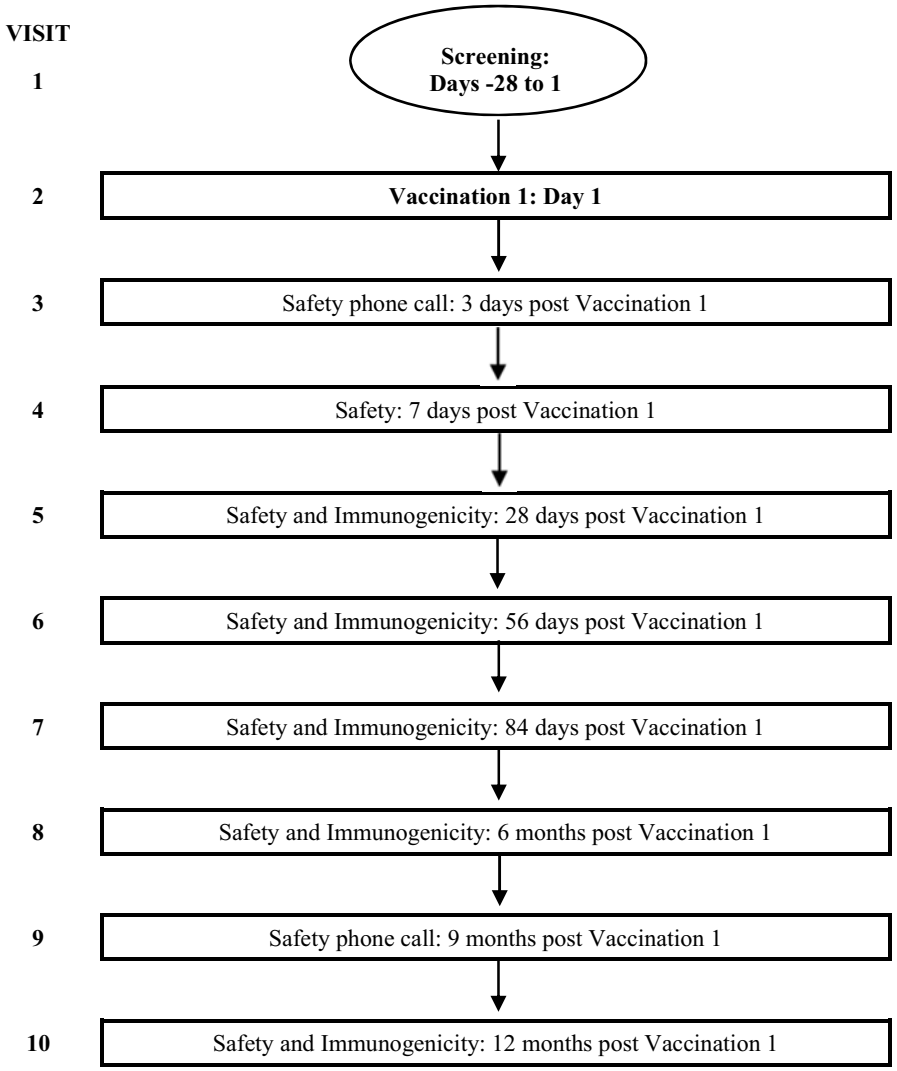
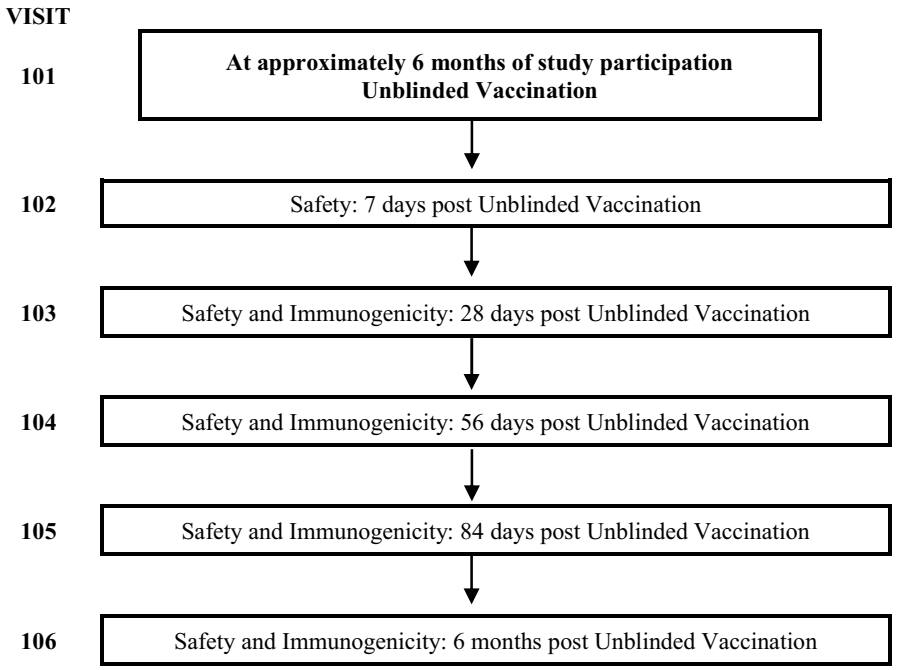


Figure 5: Schematic Overview of Groups A -C – Adolescents[a]



[a] Not applicable in Germany and the Netherlands

Figure 6: Schematic Overview of Active Vaccine Regimen for Adolescent[a] Placebo Group C



[a] Not applicable in Germany and the Netherlands

1.3. Schedule of Activities (SoA)

1.3.1. Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults[$]

Phase	Screening[a]	Study Period														
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	UB**	13	14	Exit[b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 4 mo	Inj 3 + 7 d	Inj 3 + 28 d		Inj 3 + 6 mo	Vac 2 + 12 mo	
Visit Day ±Window	-28 to 1	1	8±2[c]	15±3	29±3	57 -3/+7	64*±2[c]	71*±3	85*±3	169*±14	176*±2[c]	197*±3		337*±21	393*±21	
Visit Type	Screening	Vaccine 1	Safety	Safety and Immuno		Vaccine 2	Safety and Immuno			Antigen presentation or Placebo Injection 3[d]	Safety and Immuno		Unblind to primary vaccination regimen[t]	Safety Phone Call	Safety and Immuno	Early Exit
Written informed consent[e]	●												●			
Inclusion/exclusion criteria	●	●[1]														
Demographics	●															
Medical history/prestudy meds	●															
Physical examination[f]	●															
Pulse oximetry		●[1]														
Distribution of pulse oximeter[g]		●														
Vital signs[h] incl. body temperature	●	●[2]	●	●	●	●[2]	●	●	●	●[2]	●	●			●	●[4]
Nasal swab sample and test for SARS CoV 2 RNA	●[6]	●[7]														
Serological test for anti SARS CoV 2 antibody	●[6] 8	●[7] (8)														
Randomization		●[1]														
Unblinding													●			
Prevaccination check[i]		●[1]				●[1]				●[1]						
Urine pregnancy test[j]	●	●[1]				●[1]				●[1]						
Hematology blood sample plasma, mL[v]						●[1]5	●5	●5	●5						●5	
Hematology blood sample serum[u]		□[8]		□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]			□[8]	

Phase	Screening[a]	Study Period														
Clinic Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**UB****	**13**	**14**	**Exit[b]**
Visit Timing		**Vac 1**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 2**	**Vac 2 + 7 d**	**Vac 2 + 14 d**	**Vac 2 + 28 d**	**Vac 2 + 4 mo**	**Inj 3 + 7 d**	**Inj 3 + 28 d**		**Inj 3 + 6 mo**	**Vac 2 + 12 mo**	
Visit Day ±Window	**-28 to 1**	**1**	**8±2[c]**	**15±3**	**29±3**	**57 -3/+7**	**64*±2[c]**	**71*±3**	**85*±3**	**169*±14**	**176*±2[c]**	**197*±3**		**337*±21**	**393*±21**	
Humoral immunity (serum), blood draw, mL		●[l] 15		● 10	● 10	●[l] 10	● 10	● 10	● 10	●[l] 10	● 10	● 15			● 15	●[3]10
Cellular immunity (PBMC), blood draw, mL[k]		●[l] 60			● 60				● 60			● 60			● 60	●[3]60
Cellular immunity (whole blood, PAXgene® tubes), mL		●[l] 2.5														
Vaccination		●				●				●						
1 hour post vaccination observation[l]		●				●				●						
Solicited AE recording		*- Continuous*				*- Continuous-*				*- Continuous-*						
Unsolicited AE recording[m]		*- Continuous through +28 d-*				*- Continuous through +28 d-*				*- Continuous through +28 d-*						
SAE/AESI recording[n]		*Continuous*														●
Concomitant meds[o]		*Continuous*														●
Participant diary distribution[p]		●				●				●						
Participant diary review[q]			●				●				●					
COVID 19 like Symptom surveillance booklet and nasal swab kit training and distribution		●														
(Suspected) COVID 19 surveillance[r]		*Continuous*														
Approx. blood draw per day, mL: for participants in the PBMC subset. [for participants not in the PBMC subset]	8 [8]	77.5[s] [17.5][s]		10 [10]	70 [10]	15 [15]	15 [15]	15 [15]	75 [15]	10 [10]	10 [10]	75 [15]			80 [15]	70 [10]
Approx. cumulative blood draw, mL: for participants in the PBMC subset. [for participants not in the PBMC subset]	8 [8]	85.5[s] [25.5[s]]		95.5 [35.5]	165.5 [45.5]	180.5 [60.5]	195.5 [75.5]	210.5 [90.5]	285.5 [105.5]	295.5 [115.5]	305.5 [125.5]	385.5 [140.5]			**460.5 [155.5]**	

●[1] pre vaccination; ●[2] pre and post vaccination; ●[3] blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ●[4] if within 7 days of the previous vaccination; ●[5] if within 28 days of the last vaccination; ●[6] Screening diagnostic test for SARS CoV 2 past or current infection will be performed. ●[7] to be repeated pre vaccination if the screening test was done more than 4 days before Day 1. □[8] No extra blood required. The anti β_2 glycoprotein, anti PF4, and anti cardiolipin tests will be performed retrospectively or prospectively with blood from samples collected for the humoral immunogenicity assessment.

[$] As soon as Group 6 (placebo) participants are unblinded they should follow the procedures as outlined in the Schedule of Activities Section 1.3.4.
*The timings of visits after the second or third (ie, antigen presentation) vaccination will be determined relative to the actual day of that vaccination.
**Upon implementation of Amendment 5.

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 to continue with safety and immunogenicity follow-up visits. 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, 7 or 11, ie, 1 or 2 days prior to the 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. Antigen presentation administered as $1.25x10^{10}$ vp of Ad26.COV2.S (Groups 1-5) or placebo (Group 6).
e. Signing of the ICF should be done before any study-related activity.
f. A history-directed 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. All participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.7)
h. 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.
i. 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. 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. The investigator should also check if any other reasons, as listed in Section 7.1, Discontinuation of Study Vaccination, have been met and would prevent further study vaccination.
j. For women of childbearing potential only. Only women who are postmenopausal as defined in Section 5.1.1 (see Inclusion Criterium 6a) or who have had their uterus removed are of non-childbearing potential. All other women are considered of childbearing potential.
k. In a subset of participants in Groups 1-6.
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. Applicable from the time of local approval of protocol Amendment 5 onwards: Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure (see Section 8.3.1).

o. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
p. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
q. If an event is still ongoing on Day 8, Day 64, or Day 176 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 meets the prespecified criteria for (suspected) COVID-19 (see Section 8.1.2.1), refer to Section 1.3.7.
s. In case the screening serological test was done more than 4 days before Day 1 an additional 8 mL of blood will need to be taken (repeat of pre-vaccination test).
t. With the implementation of protocol Amendment 5, all adult participants will be unblinded, and participants who received placebo (Group 6) will start following the Schedule of Activities for the active vaccine regimen in Section 1.3.4.
u. Once protocol Amendment 4/5 is approved and implemented, hematology serum samples will be collected for all participants (see Section 10.2, Appendix 2).
v. Hematology plasma samples to be collected up to protocol Amendment 2.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; meds = medication; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; UB = unblinding visit; vac = vaccination; vp = virus particles.

1.3.2. Groups 7 and 8 (28-day interval schedule)- Adults[$]

Phase	Screening[a]	Study Period												
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	UB**	11	12	Exit[b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 4 mo	Inj 3 + 7 d	Inj 3 + 28 d		Inj 3 + 6 mo	Vac 2 + 12 mo	
Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	36*±2[c]	43*±3	57*±3	141* ±14	148*±2[c]	169*±3		309*±21	365*±21	
Visit Type	Screening	Vaccine 1	Safety	Vaccine 2	Safety and Immuno			Antigen presentation or Placebo Injection 3[d]	Safety and Immuno	Safety and Immuno	Unblind to primary vaccination regimen[s]	Safety Phone Call	Safety and Immuno	Early Exit
Written informed consent[e]	●										●			
Inclusion/exclusion criteria	●	●[1]												
Demographics	●													
Medical history/prestudy meds	●													
Physical examination[f]	●													
Pulse oximetry		●[1]												
Distribution of pulse oximeter[g]		●												
Vital signs[h] incl. body temperature	●	●[2]	●	●[2]	●	●	●	●[2]	●	●			●	●[4]
Nasal swab sample	●[6]	●[7]												
Serological test for anti SARS CoV 2 antibody	●[6] 8	●[7] (8)												
Randomization		●[1]												
Unblinding											●			
Prevaccination check[i]		●[1]		●[1]				●[1]						
Urine pregnancy test[j]	●	●[1]		●[1]				●[1]						
Hematology blood sample, plasma, mL[u]				●[1] (5)	●5	●5	●5						●5	
Hematology blood sample, serum[t]		□[8]		□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]			□[8]	
Humoral immunity (serum), blood draw, mL		●[1] 15		●[1] 10	● 10	● 10	● 10	●[1] 10	● 10	● 15			● 15	●[3] 10
Cellular immunity (whole blood, PAXgene® tubes), mL		●[1] 2.5												
Vaccination		●		●				●						
1 hour post vaccination observation[k]		●		●				●						
Solicited AE recording		*- Continuous- -*		*- - Continuous- -*				*- - - Continuous- - -*						●[4]
Unsolicited AE recording[l]		*-Continuous through +28 d-*		*- - - Continuous through +28 d- - -*				*- -Continuous through +28 d-*						●[5]
SAE/AESI recording[m]	*- - - - - Continuous- - - - -*													●

Phase	Screening[a]	Study Period												
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	UB**	11	12	Exit[b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 4 mo	Inj 3 + 7 d	Inj 3 + 28 d		Inj 3 + 6 mo	Vac 2 + 12 mo	
Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	36*±2[c]	43*±3	57*±3	141* ±14	148*±2[c]	169*±3		309*±21	365*±21	
Concomitant meds[n]		*Continuous*												●
Participant diary distribution[o]		●		●				●						
Participant diary review[p]			●		●				●					
COVID 19 like Symptom surveillance booklet and nasal swab kit training and distribution		●												
(Suspected) COVID surveillance[q]		*Continuous*												
Approx. blood draw per day, mL:	8	17.5[r]		15	15	15	15	10	10	15			20	10
Approx. cumulative blood draw, mL:	8	25.5[r]		40.5	55.5	70.5	85.5	95.5	105.5	120.5			**140.5**	

●[1] pre vaccination; ●[2] pre and post vaccination; ●[3] blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ●[4] if within 7 days of the previous vaccination; ●[5] if within 28 days of the last vaccination; ●[6] Screening diagnostic test for SARS CoV 2 past or current infection will be performed. ●[7] to be repeated pre vaccination if the screening test was done more than 4 days before Day 1. □[8] No extra blood required. The anti β_2 glycoprotein, anti PF4, and anti cardiolipin tests will be performed retrospectively or prospectively with blood from samples collected for the humoral immunogenicity assessment.

[$]As soon as Group 8 (placebo) participants are unblinded they should follow the procedures as outlined in the Schedule of Activities Section 1.3.4.
*The timings of visits after the second or third (ie, antigen presentation) vaccination will be determined relative to the actual day of that vaccination.
**Upon implementation of Amendment 5.

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 12, 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 to continue with safety and immunogenicity follow-up visits. 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, 5, or 9, ie, 1 or 2 days prior to the 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. Antigen presentation administered as 1.25×10^{10} vp of Ad26.COV2.S (Group 7) or placebo (Group 8).
e. Signing of the ICF should be done before any study-related activity.
f. A history-directed 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. All participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.7).
h. 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.

i. 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. 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. The investigator should also check if any other reasons, as listed in Section 7.1, Discontinuation of Study Vaccination, have been met and would prevent further study vaccination.
j. For women of childbearing potential only. Only women who are postmenopausal as defined in Section 5.1.1 (see Inclusion Criterium 6a) or who have had their uterus removed are of non-childbearing potential. All other women are considered of childbearing potential.
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. Applicable from the time of local approval of protocol Amendment 5 onwards: Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure (see Section 8.3.1).
n. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
o. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
p. If an event is still ongoing on Day 8, Day 36, or Day 148 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 meets the prespecified criteria for (suspected) COVID-19 (see Section 8.1.2.1), refer to Section 1.3.7
r. In case the screening serological test was done more than 4 days before Day 1 an additional 8 mL of blood will need to be taken (repeat of pre-vaccination test).
s. With the implementation of protocol Amendment 5, all adult participants will be unblinded, and participants who received placebo (Group 8) will start following the Schedule of Activities for the active vaccine regimen in Section 1.3.4.
t. Once protocol Amendment 4/5 is approved and implemented, hematology serum samples will be collected for all participants (see Section 10.2, Appendix 2).
u. Hematology plasma samples to be collected up to protocol Amendment 2.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); EUA = Emergency Use Authorization; ICF = informed consent form; meds = medication; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; UB = unblinding visit; vac = vaccination; vp = virus particles.

1.3.3. Groups 9 and 10 (84-day interval schedule) – Adults[$]

Phase	Screening[a]	Study Period													
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	UB**	12	13	Exit[b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28d	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 4 mo	Inj 3 + 7 d	Inj 3 + 28 d		Inj 3 + 6 mo	Vac 2 + 12 mo	
Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	85 -3/+7	92*±2[c]	99*±3	113*±3	197*±14	204*±2[c]	225*±3		365*±21	421*±21	
Visit Type	Screening	Vaccine 1	Safety	Safety	Vaccine 2	Safety and Immuno			Antigen presentation or Placebo Injection 3[d]	Safety and Immuno		Unblind to primary vaccination regimen[e]	Safety Phone Call	Safety and Immuno	Early Exit
Written informed consent[e]	●											●			
Inclusion/exclusion criteria	●	●[1]													
Demographics	●														
Medical history/prestudy meds	●														
Physical examination[f]	●														
Pulse oximetry		●[1]													
Distribution of pulse oximeter[g]		●													
Vital signs[h] incl. body temperature	●	●[2]	●	●	●[2]	●	●	●	●[2]	●	●			●	●[4]
Nasal swab sample	●[6]	●[7]													
Serological test for anti SARS CoV 2 antibody	●[6] 8	●[7] (8)													
Randomization		●[1]													
Unblinding												●			
Prevaccination check[i]		●[1]			●[1]				●[1]						
Urine pregnancy test[j]	●	●[1]			●[1]				●[1]						
Hematology blood sample, plasma,[u] mL					●[1](5)	●5	●5	●5						●5	
Hematology blood sample, serum[t]		□[8]		□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]			□[8]	
Humoral immunity (serum), blood draw mL		●[1] 15			●[1] 10	● 10	● 10	● 10	●[1] 10	● 10	● 15			● 15	●[3] 10
Cellular immunity (whole blood, PAXgene® tubes), mL		●[1] 2.5													

Phase	Screening[a]	Study Period													
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	UB**	12	13	Exit[b]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28d	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 + 4 mo	Inj 3 + 7 d	Inj 3 + 28 d		Inj 3 + 6 mo	Vac 2 + 12 mo	
Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	85 -3/+7	92*±2[c]	99*±3	113*±3	197*±14	204*±2[c]	225*±3		365*±21	421*±21	
Vaccination		●			●				●						
1 hour post vaccination observation[k]		●			●				●						
Solicited AE recording		- Continuous--			- -Continuous- -				- Continuous- -						●[4]
Unsolicited AE recording[l]		- - -Continuous through +28 d-			- - - -Continuous through +28 d- - - -				- - -Continuous through +28 d- - -						●[5]
SAE/AESI recording[m]		- Continuous- -													
Concomitant meds[n]		- Continuous- -													
Participant diary distribution[o]		●			●				●						
Participant diary review[p]			●			●				●					
COVID 19 like Symptom surveillance booklet and nasal swab kit training and distribution		●													
(Suspected) COVID 19 surveillance[q]		- Continuous- -													
Approx. blood draw per day, mL:	8	17.5			15	15	15	15	10	10	15			20	10
Approx. cumulative blood draw, mL:	8	25.5			40.5	55.5	70.5	85.5	95.5	105.5	120.5			140 5	

●[1] pre vaccination; ●[2] pre and post vaccination; ●[3] blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ●[4] if within 7 days of the previous vaccination; ●[5] if within 28 days of the last vaccination; ●[6] Screening diagnostic test for SARS CoV 2 past or current infection will be performed. ●[7] to be repeated pre vaccination if the screening test was done more than 4 days before Day 1. □[8] No extra blood required. The anti β_2 glycoprotein, anti PF4, and anti cardiolipin tests will be performed retrospectively or prospectively with blood from samples collected for the humoral immunogenicity assessment.

[$]As soon as Group 10 (placebo) participants are unblinded they should follow the procedures as outlined in the Schedule of Activities, Section 1.3.4.
*The timings of visits after the second or third (ie, antigen presentation) vaccination will be determined relative to the actual day of that vaccination.
**Upon implementation of Amendment 5.

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 to continue with safety and immunogenicity follow-up visits. 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, 6, or 10, ie, 1 or 2 days prior to the 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. Antigen presentation administered as $1.25x10^{10}$ vp of Ad26.COV2.S (Group 9) or placebo (Group 10).
e. Signing of the ICF should be done before any study-related activity.
f. A history-directed 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. All participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.7)
h. 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.
i. 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. 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. The investigator should also check if any other reasons, as listed in Section 7.1, Discontinuation of Study Vaccination, have been met and would prevent further study vaccination.
j. For women of childbearing potential only. Only women who are postmenopausal as defined in Section 5.1.1 (see Inclusion Criterium 6a) or who have had their uterus removed are of non-childbearing potential. All other women are considered of childbearing potential.
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. Applicable from the time of local approval of protocol Amendment 5 onwards: Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure (see Section 8.3.1).
n. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
o. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
p. If an event is still ongoing on Day 8, Day 92, or Day 204 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 meets the prespecified criteria for (suspected) COVID-19 (see Section 8.1.2.1), refer to Section 1.3.7.
r. In case the screening serological test was done more than 4 days before Day 1 an additional 8 mL of blood will need to be taken (repeat of pre-vaccination test).
s. With the implementation of protocol Amendment 5, all adult participants will be unblinded, and participants who received placebo (Group 10) will start following the Schedule of Activities for the active vaccine regimen in Section 1.3.4.
t. Once protocol Amendment 4/5 is approved and implemented, hematology serum samples will be collected for all participants (see Section 10.2, Appendix 2).
u. Hematology plasma samples to be collected up to protocol Amendment 2.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); EUA = Emergency Use Authorization; ICF = informed consent form; meds = medication; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; UB = unblinding visit; vac = vaccination; vp = virus particles.

1.3.4. Active Vaccine Regimen: Placebo Groups 6, 8 and 10 (28-day interval schedule [2-dose and single dose regimens]) – Adults

Phase	Study Period[a]							
Visit #	101	102	103	104	105	106	107	Exit
Visit Timing	with implementation of Amendment 5	Unblinded Vac 1 + 7 d	Unblinded Vacc 2	Unblinded Vac 2 + 7 d	Unblinded Vac 2 +14 d	Unblinded Vac 2 + 28 d	Unblinded Vac 1 + 6 mo	
Visit Day ±Window	UB1	UB8* ±2d[c]	UB29* -3/+7d	UB36* ±2d[c]	UB43* ±3d	UB57* ±3d	UB169* ±21d	
Visit Type	Unblinded Vaccination 1	Safety and Immuno	Unblinded Vaccination 2	Safety	Safety and Immuno	Safety and Immuno	Safety and Immuno	Early Exit
Physical examination[d]								
Vital signs[e] incl. body temperature	●[2]	●	●[2]	●	●	●	●	●[3]
Pre vaccination check[f]	●[1]		●[1]					
Urine pregnancy test[g]	●[1]		●[1]					
Hematology blood sample, plasma, mL	●[1] 5	●5	●[1] 5		● 5	●5	●5	
Hematology blood sample, serum[n]	□[5]	□[5]	□[5]		□[5]	□[5]	□[5]	
Humoral immunity (serum), blood draw, mL	●[1] 15	● 10	●[1] 10		● 10	● 10	● 15	● 10
Cellular immunity (whole blood, PAXgene® tubes), mL	●[1] 2.5							
Vaccination	●		●					
Post vaccination observation[h]	●		●					
Solicited AE recording[i]	- - - *Continuous*- - -		- - - *Continuous*- - -					●[3]
Unsolicited AE recording[j]	- - - *Continuous through +28 d*- - -			- - - *Continuous through +28 d*- - -				●[4]
SAE/AESI recording[j]	- - - - - - - *Continuous*- - - - - - -							●
Concomitant meds[k]	- - - - - - - *Continuous*- - - - - - -							●
Participant diary distribution[o]	●		●					
Participant diary review[l,m]		●		●				●[3]
(Suspected) COVID 19 surveillance[q]	- *Continuous*- -							
Approx. blood draw per day, mL:	22.5	15	15		15	15	20	10
Approx. cumulative blood draw, mL (Group 6)[o]: for participants in the PBMC subset. [for participants not in the PBMC subset]	483.0 [178]	498.0 [193]	513.0 [208]		528.0 [223]	543.0 [238]	563.0 [258]	
Approx. cumulative blood draw, mL (Groups 8 & 10)[p]:	163	178	193		208	223	243	

●[1] pre vaccination; ●[2] pre and post vaccination; ●[3] if within 7 days of the previous vaccination; ●[4] if within 28 days of the last vaccination; □[5] No extra blood required. The anti β_2 glycoprotein, anti PF4, and anti cardiolipin tests will be performed retrospectively or prospectively with blood from samples collected for the humoral immunogenicity assessment.

a. If a participant shows COVID-19 like symptoms, the participant should contact the site for guidance and must follow their local country and site level recommendations for COVID-19.
b. For those participants who are unable to continue participation in the study up to Visit 15 or 19 (depending on the vaccination regimen), but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who no longer wish to receive study vaccination (see Section 7.1) will be offered all safety and immunogenicity follow-up visits according to the current Schedule of Activities. 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 14 or 16, 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.
d. An abbreviated, symptom-directed examination may be performed if determined necessary by the investigator.
e. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
f. Investigator must check for acute illness or body temperature ≥38.0°C/100.4°F at the time of vaccination. If any of these events occur at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows. 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. The investigator should also check if any other reasons, as listed in Section 7.1, have been met and would prevent further study vaccination.
g. For women of childbearing potential only. Only women who are postmenopausal as defined in Section 5.1.1 (see Inclusion Criterium 6a) or who have had their uterus removed are of non-childbearing potential. All other women are considered of childbearing potential.
h. Participants will be closely observed for a at least 1 hour post-vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
i. AEs and special reporting situations that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post vaccination.
j. All SAEs related to study procedures or non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure. Applicable from the time of local approval of protocol Amendment 5 onwards: Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure (see Section 8.3.1).
k. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1. Concomitant therapies associated with an SAE meeting the criteria outlined in Section 10.3.1 will be collected and recorded in the eCRF from the moment of 1st vaccination through the end of the study.
l. Participants should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
m. If an event is still ongoing on UB8 or Day UB36 the participant should continue to collect information in the reactogenicity diary until resolution. The reactogenicity diary should be reviewed again at the next visit.
n. Once protocol Amendment 4/5 is approved and implemented, serum samples will be collected for all participants (see Section 10.2, Appendix 2).
o. Starting at 460.5 and 155.5 mL at the time of the Unblinding visit in the PBMC and non-PBMC subsets, respectively, per Schedule 1.3.1.
p. Starting at 140.5 mL at the time of the Unblinding visit per Schedule 1.3.2 and 1.3.3.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); meds = medication; m = months; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; UB = unblinding; Vac = vaccination.

1.3.5. Groups A to C Adolescents[a]

Phase	Screening[a]	Study Period										
Clinic Visit #	1	2	3	4	5	6	7		8	9	10	Exit[b]
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 1 + 84 d		Vac 1 + 6 mo	Vac 1 + 9 mo	Vac 1 + 12 mo	
Visit Day ±Window	-28 to 1	1	4	8±2[c]	29±3	57 3/+7	85*±3		169±3	253±21	337*±14	
Visit Type	Screening	Vaccine 1	Safety Phone Call[t]	Safety	Safety and Immuno	Safety and Immuno	Safety and Immuno		Safety and Immuno	Safety Phone Call	Safety and Immuno	Early Exit
Written informed consent/assent[d]	●							Unblind to primary vaccination regimen[s]				
Inclusion/exclusion criteria	●	●[1]										
Demographics	●											
Medical history/prestudy meds	●											
Physical examination[e]	●											
Pulse oximetry		●[1]										
Distribution of pulse oximeter[f]		●										
Vital signs[g] incl. body temperature	●	●[2]		●	●	●[2]	●		●		●	●[4]
Nasal swab sample and test for SARS CoV 2 RNA	●[6]	●[7]										
Serological test for anti SARS CoV 2 antibody	●[6] 8	●[7] 8										
Randomization		●[1]										
Prevaccination check[h]		●[1]										
Urine pregnancy test[i]	●	●[1]										
Humoral immunity (serum), blood draw, mL		●[1] 7.5			● 7.5	●[1] 10	● 10		● 10		● 10	●[3] 10
Cellular immunity (whole blood, PAXgene® tubes), mL		●[1] 2.5			● 2.5							
Vaccination		●										
1 hour post vaccination observation[k]		●										
Solicited AE recording		- - Continuous- -										●[4]
Unsolicited AE recording[l]		- - - Continuous through +28 d- - -										●[5]
SAE/AESI recording[m]		- Continuous- -										●

[a] Not applicable in Germany and the Netherlands

Phase	Screening[a]	Study Period									
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	Exit[b]
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 1 + 84 d	Vac 1 + 6 mo	Vac 1 + 9 mo	Vac 1 + 12 mo	
Visit Day ±Window	-28 to 1	1	4	8±2[c]	29±3	57 3/+7	85*±3	169±3	253±21	337*±14	
Concomitant meds[n]		*Continuous*									●
Participant diary distribution[o]		●									
Participant diary review[p]			●	●							
COVID 19 like Symptom surveillance booklet and nasal swab kit training and distribution		●									
(Suspected) COVID 19 surveillance[q]		*Continuous*									
Approx. blood draw per day, mL:	8	10[r]			10	10	10		10		10	10
Approx. cumulative blood draw, mL:	8	18[r]			28	38	48		58		68	

●[1] pre vaccination; ●[2] pre and post vaccination; ●[3] blood samples for immunogenicity will only be taken if the early exit visit is at least 10 days after the previous immunogenicity blood draw; ●[4] if within 7 days of the previous vaccination; ●[5] if within 28 days of the last vaccination; ●[6] Screening diagnostic test for SARS CoV 2 past or current infection will be performed. ●[7] to be repeated pre vaccination if the screening test was done more than 4 days before Day 1

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 the last visit, but for whom consent/assent is not withdrawn, 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 to continue with safety and immunogenicity follow-up visits. Participants who wish to withdraw consent/assent 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 (ie, 1 or 2 days prior to the 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/assent should be done before any study-related activity.
e. A history-directed 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. All participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.7)
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. 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. The investigator should also check if any other reasons, as listed in Section 7.1, Discontinuation of Study Vaccination, have been met and would prevent further study vaccination.

i. For participants of childbearing potential only. Only women who are postmenopausal as defined in Section 5.1.2 (see Inclusion Criterium 6a) or who have had their uterus removed are of non-childbearing potential. All other women are considered of childbearing potential.
j. In a subset of participants.
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 moment of vaccination until completion of the participant's last study-related procedure.
n. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.
o. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant.
p. If an event is still ongoing 7 days after vaccination, 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 meets the prespecified criteria for (suspected) COVID-19 (see Section 8.1.2.1), refer to Section 1.3.7.
r. In case the screening serological test was done more than 4 days before Day 1 an additional 8 mL of blood will need to be taken (repeat of pre-vaccination test).
s. With the implementation of Amendment 6 (at approximately 6 months of study participation), all adolescent participants and investigators will be unblinded (ie, informed whether they received placebo or Ad26.COV2.S) and the study will continue as an open-label study. The site staff may be unblinded up to 7 days before the scheduled Unblinded visit date to allow for appropriate planning and preparations to take place. Participants who received active vaccine (Groups A and B) will continue to follow this schedule. Participants who received placebo (Group C) will complete Visit 8 activities, including a coagulopathy blood draw to take place at the same time as the blood draw for humoral immunity, after which they will start following the Schedule of Activities for the active vaccine regimen in Section 1.3.6. Note that assessments on Visit 8 are to be performed for all participants, irrespective of the unblinding outcome.
t. Telephone contact on Day 4 post vaccination for the 11 sentinel participants, with diary review during phone call.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); EUA = Emergency Use Authorization; ICF = informed consent form; meds = medication; mo = months; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination; vp = virus particles.

1.3.6. Active Vaccine Regimen: Placebo Group C – Adolescents[a]

Phase	Study Period[a]						
Visit #	101	102	103	104	105	106	Exit[b]
Visit Timing	With implementation of Amendment 6 (At Approximately 6 months of Study Participation)	Unblinded Vac 1 + 7 d	Unblinded Vac 1 + 28 d	Unblinded Vac 1 +56 d	Unblinded Vac 1 + 84 d	Unblinded Vac 1+6 mo	
Target Visit Day ±Window	169* -3/+7	176*±2[c]	197*±3	225*-3/+7	253*±3[c]	337*±3	
Visit Type	Unblinded Vaccination 1	Safety	Safety and Immuno	Safety and Immuno	Safety and Immuno	Safety and Immuno	Early Exit
Physical examination[d]							
Vital signs[e] incl. body temperature	●[2]	●	●	●[2]	●	●	●[3]
Prevaccination check[f]	●[1]						
Urine pregnancy test[g]	●[1]						
Humoral immunity (serum), blood draw, mL	□[5]		●7.5	● 10	●10	●10	
Clinical laboratory blood sample[n]	●5.6						
Hematology blood sample, serum	□[6]		□[6]	□[6]	□[6]	□[6]	
Cellular immunity (whole blood, PAXgene® tubes), mL	●[1] 2.5		●2.5				
Vaccination	●						
Post vaccination observation[h]	●						
Solicited AE recording	--- *Continuous*---						●[3]
Unsolicited AE recording[i]		--- *Continuous through +28 d*---					●[4]
SAE/AESI recording[j]	---------- *Continuous*----------						●
Concomitant meds[k]	---------- *Continuous*----------						●
Participant diary review[l,m]		●					●[3]
Approx. blood draw per day, mL:	8.1		10			10	10
Approx. cumulative blood draw, mL[o]	66.1		76.1			86.1	

●[1] pre vaccination; ●[2] pre and post vaccination; ●[3] if within 7 days of the previous vaccination; ●[4] if within 28 days of the last vaccination; □[5] No extra blood required. Blood from samples collected for the humoral immunogenicity assessment are described in the Unblinding visit in Schedule 1.3.5. □[6] No extra blood required. Anti PF4 will be performed with blood from samples collected for the humoral immunogenicity assessment at the same timepoint.

[a] Not applicable in Germany and the Netherlands

a. If a participant shows COVID-19 like symptoms, the participant should contact the site for guidance and must follow their local country and site level recommendations for COVID-19.
b. For those participants who are unable to continue participation in the study up to Visit 106, but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who no longer wish to receive study vaccination (see Section 7.1) will be offered all safety and immunogenicity follow-up visits according to the current Schedule of Activities. 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 102, 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.
d. An abbreviated, symptom-directed examination may be performed if determined necessary by the investigator.
e. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
f. Investigator must check for acute illness or body temperature ≥38.0°C/100.4°F at the time of vaccination. If any of these events occur at the scheduled time for vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows. 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. The investigator should also check if any other reasons, as listed in Section 7.1, have been met and would prevent further study vaccination.
g. For women of childbearing potential only. Only women who are postmenopausal as defined in Section 5.1.2 (see Inclusion Criterium 6a) or who have had their uterus removed are of non-childbearing potential. All other women are considered of childbearing potential.
h. Participants will be closely observed for a at least 1 hour post vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 1-hour post-vaccination observation period is complete.
i. AEs and special reporting situations that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post vaccination.
j. All SAEs related to study procedures or non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure
k. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1. Concomitant therapies associated with an SAE meeting the criteria outlined in Section 10.3.1 will be collected and recorded in the eCRF from the moment of 1st vaccination through the end of the study.
l. Participants should keep the diary after the review and continue to collect information until resolution. The diary should be reviewed again at the next visit.
m. If an event is still ongoing at Visit 102, the participant should continue to collect information in the diary until resolution. The diary should be reviewed again at the next visit.
n. Whole blood samples will be used for complete blood cell count, including platelet count, in a local laboratory or substitute for local laboratory, depending on local feasibility towards turnaround time of sample processing. Results should be available within 72 hours. The division of volumes between whole blood, plasma and serum is described in the laboratory manual. Serum and plasma are to be stored for future testing to evaluate the impact of any potential thromboembolic events. Samples can also be tested for anti-PF4 antibodies and platelet activation assay (if HIT/PF4 is positive). Unused samples may be used for immunogenicity testing.
o. Starting at 58 mL at the time of the Unblinding visit per Schedule 1.3.5.

AE = adverse event; COVID-19 = coronavirus disease-2019; d = day(s); meds = medication; m = months; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; Vac = vaccination.

1.3.7. Procedures for Participants With (Suspected) COVID-19 – Adults and Adolescents[a]

Timing relative to onset of trigger	COVID-19 Day 1	COVID-19 Days 1-4	COVID-19 Days 3-8[a]	COVID-19 Days 29 ± 7d[a]	Until resolution[b]
Trigger: Participant to contact study site as soon as any signs or symptoms of possible COVID 19 occur/at time of becoming aware of positive RT PCR test	●				
Nasal swab[c]		●[3]	*Twice weekly or more frequently* [1]		
Physical examination[d]			●	●	
Vital signs[e] including body temperature			●	●	
Humoral immunity (serum), mL			● 15 or 7.5[i]	● 15 or 7.5[i]	
RNA seq (whole blood, PAXgene tube), mL			● 2.5	● 2.5	
Body temperature[f]		●[2]			
Symptoms of Infection with Coronavirus 19 (SIC)[g]		●[2]			
Study site personnel to contact participant[h]		*Weekly or more frequently*			
Pulse oximetry by site staff			●		
Pulse oximetry by the participant (to be completed by the participant in the provided booklet)		*3 times a day*			

[1] Nasal swabs to be obtained following the same procedures as the first nasal swab. ●[2] If either nasal swab is positive for SARS-CoV-2, collection of data will continue until resolution. ● [3] Not needed if the trigger was a positive RT-PCR test.

a. A study visit will be conducted 3-8 days after trigger onset. A study visit will be conducted 28 days (±7 days) after trigger onset for participants with a positive test result for SARS-CoV-2 infection.

b. Defined as having 2 consecutive days with no COVID-19-related signs or symptoms AND 2 consecutive negative nasal swabs. The sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

c. If the trigger was a sign or symptom: a nasal swab should be collected by 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 (see Section 8.1.2.1, Prespecified Criteria for (Suspected) COVID-19. As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgment is required to exclude vaccine-related events). The site should arrange the transfer of the sample to the study site as soon as possible after sample collection. It is preferred that the swab is taken by a caregiver (spouse, partner, relative, friend, or health care professional). If that is not possible, the participant can collect the swab himself or herself. If the trigger was a positive RT-PCR test, then this first nasal swab is not needed. A second nasal swab will be obtained on COVID-19 Day 3-8 following the same procedures as the first nasal swab. The second nasal swab may also be collected at home, at the hospital, or at another location, if needed, by a study site staff, if appropriate procedures are in place. The presence of SARS-CoV-2 infection will be assessed at the study site by molecular testing using the nasal swab samples. The nasal swabs may be tested at the central laboratory for the presence of SARS-CoV-2 and other respiratory pathogens using a broad respiratory pathogens panel. From COVID-19 Day 3-8 onwards: Once a first negative swab is obtained, a second swab should be taken as soon as possible, but with a minimum of 1 day between the 2 swabs. This should be repeated until 2 consecutive negative swabs are obtained.

d. An abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

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

[a] Not applicable in Germany and the Netherlands

f. Participant should measure body temperature daily and record the highest temperature each day.
g. Participants should complete the SIC starting on the first day of trigger onset See Section 10.7 for an example of the SIC.
h. If a participant has a positive test result for SARS-CoV-2 infection, the participant will be notified and 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 SIC will be reviewed by study staff during these contacts (phone call or visit).
i. 15 mL for adults. 7.5 mL for adolescents. The sponsor recommends to follow these participants until 2 consecutive negative nasal swabs could be obtained.

COVID-19 = coronavirus disease-2019; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptom of Infection with COVID-19.

1.3.8. Participants with a Suspected AESI – Adults and Adolescents

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[0], British Society of Haematology Expert Haematology Panel[0], and the CDC[0]). 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 Janssen Adjudication Committee.

In the event of a suspected thrombotic event or TTS, laboratory assessments are required to facilitate diagnosis and determine treatment options, including but not limited to platelet count and 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 suspected AESI[c]	●	
Clinical lab blood sample (whole blood), mL[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.
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. Whole blood samples will be used for a platelet count (as part of a complete blood count, if applicable) in a local laboratory or substitute for local laboratory, depending on local feasibility towards turnaround time of sample processing. Serum and plasma samples will be derived from the whole blood sample for coagulation-related testing in a central laboratory (see Section 10.2, Appendix 2). For the follow-up visit, the volume of blood to be collected may vary depending on the clinical evaluation of the case.
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 10.13, Appendix 13 for further details.
f. Refer to Section 6.9 for collection and recording of concomitant therapies associated with a suspected AESI.

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

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) spike (S) protein, which will be assessed in this study.

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.[0]

The term "study vaccine" throughout the protocol refers to Ad26.COV2.S or placebo as defined in Section 6.1, Study Vaccinations Administered. Scientifically, the administration of the Ad26.COV2.S $1.25x10^{10}$ virus particles (vp) or placebo dose 4 months after the primary vaccination regimen is considered as presentation of antigen. Nevertheless, for the sake of simplicity, the terms "study vaccine" and "vaccination" throughout the protocol encompass administration of the antigen presentation dose. 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."

The term "legal guardian" used throughout the document refers to the parent(s) (preferably both if available or as per local requirements), legally appointed guardian(s), or legally acceptable representative(s), as defined by national and local laws and regulations, who consent(s) on behalf of the minor child (participant). For the purposes of this study, all references to participants refers to the participants (child) and his or her legal guardian(s) (as defined above) who have provided consent (and assent as applicable) according to the Informed Consent Process and Assent Form described in Section 10.3.3.

Study VAC31518COV2001 is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V.) in collaboration with the United States (US) government and the COVID-19 Response Team (formerly Operation Warp Speed), which also encompasses the Biomedical Advanced Research and Development Authority, the National Institutes of Health, and the COVID-19 Prevention Trials Network.

COVID-19 Vaccine and Considerations

Currently, there is only limited availability of authorized/licensed vaccines for the prevention of coronavirus disease-2019 (COVID-19). The continued development of safe and effective vaccines 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.[0,0] 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.[0,0,0] 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 1 dose, in both naïve and pre-immune individuals (RSV). These antibodies may persist for a year or more (RSV) after a single vaccination in pre-immune participants. They have functional properties of neutralization (RSV, Zika), crystallizable fragment (Fc)-mediated antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (HIV, malaria). Furthermore, these data support an immunogenicity profile with emphasis on T-helper cell type 1 (Th)1 responses and demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in cluster of differentiation (CD) 4^+ and $CD8^+$ T cells.[0,0,0]

Ad26.COV2.S Candidate Vaccine

The aim of the COVID-19 vaccine clinical development program is to develop a safe and effective vaccine for the prevention of COVID-19. The candidate vaccine to be assessed in this study is Ad26.COV2.S, which is a recombinant, replication-incompetent Ad26 encoding a prefusion stabilized variant of the SARS-CoV-2 S protein. The parental S protein sequence was derived from a SARS-CoV-2 clinical isolate (Wuhan, 2019, whole genome sequence NC_045512). The selection of antigen was based on previous work on the SARS-CoV and MERS-CoV candidate vaccines.[0,0,0] The S protein is the major surface protein on coronaviruses and is responsible for binding to the host cell receptor and mediating the fusion of host and viral membranes, thereby facilitating virus entry into the cell.[0] In this study, different vaccination intervals and multiple

lower dose levels compared to the dose levels in the first-in-human study (VAC31518COV1001) will be assessed.

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

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus.[0,0] It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019.[0] Early epidemiological investigations suggested that the majority of early cases were linked to a seafood market, with patients infected through zoonotic or environmental exposure, followed by the subsequent spread of infection by human-to-human transmission among close contacts.[0] However, there is some controversy about the initial origin of the virus.[0] 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.[0,0] 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.[0]

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.[0,0] As of October 21, 2020, approximately 40,792,599 cases of COVID-19 and approximately 1,124,918 COVID-19-related deaths have been reported.[0]

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.[0] Severe clinical presentations have been reported in as many as 20% to 25% of laboratory-confirmed cases.[0] 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%).[0] 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%).[0] Lymphopenia occurred in 70.3% of patients, and chest CT scans showed bilateral patchy shadows or ground-glass opacities in the lungs of all patients. Thirty-six patients (26%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome, arrhythmia, and shock. Subsequent US Centers for Disease Control and Prevention (CDC) descriptions of COVID-19 clinical case definitions[0] and Janssen-sponsored interviews with COVID-19-experienced clinicians have included signs and symptoms of respiratory distress such as blue lips, extreme shortness of breath and dyspnea, persistent cough, deep vein thrombosis (DVT), Kawasaki-like disease, discoloration of feet and toes, chills, shaking chills, loss of sense of taste and smell, signs of stroke, disorientation, inability to respond or understand verbal communication, among others.

At present, it appears that individuals aged ≥65 years, especially those with comorbid diseases, are subject to the highest incidence of morbidity and mortality.[0] 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.[0] However, young children, particularly infants, were susceptible to severe disease, with the highest proportion of severe and critical cases by age group reported for children aged <1 year (10.6% of cases in this age group). A study of 149,082 COVID-19 cases reported in the US was consistent with these findings.[0] Only 1.7% of these cases occurred in persons aged <18 years, although this age group accounts for 22% of the US population. Furthermore, relatively few pediatric COVID-19 cases were hospitalized, indicating that COVID-19 might have a mild course among younger patients. Hospitalization was most common among pediatric patients aged <1 year and those with underlying conditions. Recent (April-May 2020) reports describe several cases of multisystem inflammatory syndrome (MIS) in children with Kawasaki disease-like features (ie, fever, laboratory markers of inflammation, severe illness requiring hospitalization, multisystem organ involvement). Most of these children had tested positive for current or recent SARS-CoV-2 infection or were linked to a COVID-19 case. It is currently unknown if MIS is specific to children or if it may also occur in adults.[0,0]

More recently, it has been observed that although the rate of hospitalizations due to COVID-19 is lower in children than in adults, the burden of the hospitalizations is similar to that caused by other diseases that can be prevented by vaccination.[0] In addition, evidence points to Hispanic and Black children likely being at increased risk for severity of COVID-19 infection.[0,0,0]

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.[0] The first known cases of severe acute respiratory syndrome (SARS) occurred in Southern China in November 2002.[0] 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 multiorgan failure in June 2012.[0] MERS-CoV is considered to be a zoonotic virus capable of nonsustained human-to-human transmission. Since 2012, sporadic cases and community and health-care-associated clusters of infected individuals have been reported in the Middle East.

Patients with SARS or MERS present with various clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory disease with extrapulmonary manifestations.[0,0] 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.[0,0] The case-fatality rate of MERS-CoV infections is estimated to be 35%.[0]

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

The sponsor is developing a COVID-19 vaccine based on a human replication-incompetent Ad26 vector encoding the SARS-CoV-2 S protein. The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate coronavirus vaccines against SARS-CoV (2002-2003 outbreak), and the common conclusion that has emerged from the evaluation of several different vaccines is that the viral S protein is the only significant target for neutralizing antibodies[0,0,0,0] and the only viral protein that can elicit protective immunity in animal models.[0,0,0,0,0] Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen.

2.1. Study Rationale

Detailed information about the rationale for the selected doses can be found in Section 4.3 Justification for Dose.

Adults

In this study, safety and immunogenicity responses following 2-dose ($5x10^{10}$ vp, $2.5x10^{10}$ vp, $1.25x10^{10}$ vp) and single-dose ($5x10^{10}$ vp, $1x10^{11}$ vp) primary vaccination regimens will be assessed in adults aged 18 to 55 years inclusive, and adults in good or stable health aged 65 years and older, to investigate dose sparing measures resulting in an increase of the number of vaccine doses available in a pandemic context. Safety and immunogenicity of 28-, 56-, and 84-day vaccination intervals for the 2-dose regimen ($5x10^{10}$ vp) will also be assessed to gather insight on the possible compression and delay of the vaccination schedule, as this may be of interest in an emergency use setting.

The $5x10^{10}$ vp dose level is administered in the Phase 3 efficacy studies VAC31518COV3001 (1-dose regimen) and VAC31518COV3009 (2-dose regimen).

In addition, an assessment of the immunogenicity of the $1.25x10^{10}$ vp Ad26.COV2.S dose level that is representative of the vaccine titer at the end of the foreseen shelf-life for the $5x10^{10}$ vp dose level in the context of emergency use with storage at 2-8 °C will be done. By lowering the dose level (ie, to $2.5x10^{10}$ vp and $1.25x10^{10}$ vp), there will also be a potential to immunobridge to a lower dose level regimen, should the efficacy study (VAC31518COV3001) provide evidence of an immune correlate of protection.

And finally, the anamnestic response after 7 days following a low-dose antigen presentation ($1.25x10^{10}$ vp Ad26.COV2.S) as a surrogate of antigen exposure upon SARS-CoV-2 infection,

after the primary 2-dose or single-dose vaccination regimens, will be assessed in adult Groups 1-5, 7 and 9.

Adolescents

Available platform data, as well as safety data from the VAC31518COV1001 study, (see Section 2.2 and Section 2.3.1) support initiating evaluation of Ad26.COV2.S in adolescents aged 12 to 17 years, inclusive. In order to generate data in adolescents that will allow the use of a vaccine to prevent COVID-19 in this age group, the safety and immunogenicity responses following primary vaccination regimens will also be assessed in adolescents aged 12 to 17 years, inclusive.

2.2. Background

Nonclinical Pharmacology

Nonclinical studies were performed to test the immunogenicity of different vaccine candidates, leading to the selection of the current vaccine for this development program. In addition, vaccine efficacy of Ad26.COV2.S has been shown in Syrian hamsters and NHP. Details are provided in the IB.[0]

Nonclinical Safety

Biodistribution

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

Toxicology

The sponsor has significant nonclinical experience with Ad26-vectored vaccines using various transgenes encoding HIV, RSV, Ebola virus, filovirus, human papilloma virus, Zika, influenza (universal flu [Uniflu]), and malaria antigens. To date, more than 10 Good Laboratory Practice (GLP) combined repeated dose toxicology and local tolerance studies have been performed in rabbits (and 1 study in rats), testing the nonclinical safety of various homologous and heterologous regimens with Ad26-based vaccines at full human dose levels up to 1.2×10^{11} vp. No adverse effects have been observed in these studies. The vaccine-related effects observed were similar across studies, considered to be reflective of a physiological response to the vaccines administered, and seem to be independent of the antigen transgene. Overall, there were no safety signals detected

in any of the available GLP toxicology studies with Ad26-based vaccines up to the highest dose level tested (1.2×10^{11} vp). In a combined embryo-fetal and pre- and postnatal development GLP study in female rabbits with another Ad26-based vaccine (Ad26.ZEBOV, encoding an Ebola virus antigen), there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period. A repeated dose and local tolerance GLP study, and a combined embryo-fetal and pre- and postnatal development GLP study with Ad26.COV2.S are planned to run in parallel with study VAC31518COV1001.

Clinical Studies

At the time of initial protocol writing, no clinical data with the Ad26.COV2.S vaccine were available. At this stage of protocol Amendment 2, initial immunogenicity and safety data (28 days post-Dose 1 data from Cohort 1a (participants aged ≥18 to ≤55 years) and available data from Cohort 3 (participants aged ≥65 years) from study VAC31518COV1001 have become available and demonstrate that a single dose of Ad26.COV2.S at 5×10^{10} virus particles (vp) and 1×10^{11}vp induces an immune response that meets prespecified minimum criteria and has an acceptable safety profile. Data from study VAC31518COV1001 supports the evaluation of Ad26.COV2.S vaccine in younger age groups. A dose escalation approach will be used in the present study.

Refer to the latest IB[0] and its addenda (if applicable) for a high level description of the additional ongoing studies with Ad26.COV2.S.

Clinical Safety Experience With Ad26-based Vaccines

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

As of 04 September 2020, Ad26-based vaccines have been administered to approximately 114,000 participants in ongoing and completed studies, including more than 99,000 participants in an ongoing Ebola vaccine study in the Democratic Republic of the Congo (VAC52150EBL3008/DRC-EB-001), and an ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign).

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

As of 04 September 2020, more than 109,000 participants were enrolled in ongoing studies and in the ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign). However, their safety data were not included in the AdVac® safety database report V5.0 because

the studies were still blinded, the studies were unblinded but their analysis took place after the AdVac® safety database report cut-off date, or the study data were not integrated in the Ad26-based vaccine database used for the report.

Overall, the Ad26-based vaccines were well tolerated, irrespective of the antigen transgene, without significant safety issues identified to date. See Section 2.3.1, 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 in participants aged ≥60 years, including the Phase 1 studies VAC18193RSV1003 and VAC18193RSV1005, Phase 1/2a study VAC18193RSV1004, Phase 2a study VAC18193RSV2003, and Phase 2b study VAC18193RSV2001. Up to a cut-off date of 24 April 2020, approximately 3,700 participants aged ≥60 years have received an Ad26.RSV.preF-based regimen in completed and ongoing studies. An acceptable safety and reactogenicity profile in participants aged ≥60 years has been reported for the Ad26.RSV.preF-based regimens assessed in these studies, and no safety concerns have been raised to date.

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

In the 1960s, a formalin-inactivated (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.[0,0,0,0] Although the mechanisms for ERD are not fully understood, it is thought that the FI-RSV vaccine 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 T helper cell (Th) type 2-skewed type T-cell response.[0] Vaccine-induced ERD has also been described for SARS-CoV and MERS-CoV in some animal models in which candidate vaccines induced a Th2 biased immune response,[0,0,0,0,0,0] but proof of human SARS-CoV or MERS-CoV vaccine-associated enhanced disease does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. For SARS and MERS, the mechanism of enhanced disease observed in mice has been associated with a Th2-mediated eosinophilic infiltration in the lung, which is reminiscent of ERD effects observed after RSV infection of mice immunized with FI-RSV. Similar to RSV vaccines, enhanced disease has been shown for whole-inactivated SARS-CoV vaccines, as well as subunit vaccines inducing a Th2-type immune response, which can be rescued by formulating vaccines in Th1-skewing adjuvants. In addition to a Th1-biased immune response, also induction of a high proportion of neutralizing antibodies compared with virus binding antibodies is desirable to prevent predisposition to enhanced disease as observed for RSV vaccines. While vaccine-associated enhanced disease was observed in nonclinical studies with experimental SARS and MERS vaccines, it is not a given that the same risk applies to COVID-19 vaccines. To the sponsor's knowledge, antibody-related COVID-19 disease enhancement has not been observed in nonclinical models yet. Antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 were shown not to enhance in vitro infectivity. Repeated SARS-CoV-2 challenge of NHP or NHP studies with Th2 biasing COVID-

19 vaccines that would be expected to predispose to enhanced disease did not show any signs of enhanced disease. In addition, disease enhancement was not observed in NHP immunized with ChAdOx1 encoding SARS-CoV-2 S protein prior to challenge with SARS-CoV-2.[0] The Ad26 vector was chosen due to its ability to induce humoral and strong cellular responses with a Th1 immune phenotype.[0,0,0,0,0,0,0,0,0,0] This type 1 polarity of the immune response minimizes the risk of enhanced disease after SARS-CoV-2 infection.

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.[0,0,0] In the RSV vaccine clinical development program, Ad26.RSV.preF was 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 a favorable Th1 bias, was confirmed. In August 2020, the study had been completed and showed that Ad26.RSV.preF had an acceptable safety and reactogenicity profile. 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 vaccination.

Ad26-based Vaccines in the Pediatric Population

Ad26.RSV.preF in Toddlers: see above under subheading of Th1/Th2 profile.

Ad26.ZEBOV in Children and Adolescents

ZABDENO® (Ad26.ZEBOV; suspension for injection) was recently approved in the EU, as part of the ZABDENO, MVABEA® (MVA-BN-Filo; suspension for injection) vaccine regimen indicated for active immunization for prevention of disease caused by Ebola virus (*Zaire ebolavirus* species) in individuals ≥1 year of age (ZABDENO SmPC, 2020).

Adverse reactions following ZABDENO vaccination reported in children 1 to 17 years of age are provided in Table 1.

Table 1: Adverse Reactions Reported in Children 1 to 17 Years of Age Following Vaccination with ZABDENO

System Organ Class	Frequency	Adverse Reaction
Metabolism and nutrition disorders	very common	decreased appetite
Psychiatric disorders	very common	irritability
Gastrointestinal disorders	common	vomiting, nausea
Musculoskeletal and connective tissue disorders	common	arthralgia, myalgia
General disorders and administration site conditions	very common	Fatigue, decreased activity, injection site pain
	common	Pyrexia, injection site pruritus, injection site swelling, injection site erythema

The approval of ZABDENO in pediatric individuals was based on pooled safety data from 2 Ebola clinical studies (Phase 2 study VAC52150EBL2002 and Phase 3 study VAC52150EBL3001). A total of 839 participants are included in this pooling of which 649 participants (253 aged 12 to 17 years, 252 aged 4 to 11 years and 144 aged 1 to 3 years) received the Ad26.ZEBOV ($5x10^{10}$ vp) vaccine as Dose 1 of the heterologous Ebola vaccine regimen, which also includes MVA-BN-Filo ($1x10^{8}$ infectious units [Inf.U]) as Dose 2, with an interval of at least 28 days between the doses. In these studies, 189 participants were enrolled to receive the control regimen (placebo [N 45] or active control [MenACWY; N 144]).

No deaths, serious adverse events (SAEs) considered related to study vaccine or adverse events (AEs) leading to discontinuation were reported in children or adolescents.

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.[0]

2.3.1 Risks Related to Study Participation

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

Interim analyses after the first dose of blinded safety data from approximately 800 participants of 18-55 years of age and 65 years and older in study COV1001 showed that local AEs were observed in 58% and 27% of participants, respectively. Solicited systemic AEs were reported in 64% and 36% of participants, respectively. Fevers occurred in both cohorts in 19% (5% Grade 3) and 4% (0% Grade 3), respectively, were mostly mild or moderate, and resolved within 1 to 2 days after vaccination. The most frequent local AE was injection site pain and the most frequent solicited AEs were fatigue, headache and myalgia. The safety and reactogenicity profiles of 2 dose levels, $5x10^{10}$ vp and $1x10^{11}$ vp were considered acceptable.

For the most comprehensive nonclinical information regarding Ad26.COV2.S, refer to the latest version of the IB.[0]

Sites should advise participants that side effects include fever as well as injection site pain, headache, fatigue, myalgia, and nausea per the current ICF.

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 approximately 1-2 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[0], British Society of Haematology - Expert Haematology Panel[0], CDC[0]). 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 Janssen 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 and Section 8.3.6.1), which may facilitate diagnosis and clinical management of the event.

Risks Related to Adenoviral-vectored Vaccines

The clinical AdVac® safety database (report version 5.0, dated 10 April 2020, cut-off date 20 December 2019) contains pooled safety data from 26 Janssen-sponsored clinical studies with Ad26 vaccine candidates: Ad26.ZEBOV (Ebola; 10 studies), Ad26.ENVA.01, Ad26.Mos.HIV and Ad26.Mos4.HIV (HIV; 8 studies), Ad26.CS.01 (malaria; 1 study), Ad26.RSV.FA2 and Ad26.RSV.preF ([RSV; 6 studies), and Ad26.Filo (filovirus; 1 study). In these studies, 4,224 adult participants and 650 children received at least 1 vaccination with an Ad26-based vaccine. The AdVac® safety database report includes data only from studies for which the database has been locked for the final analysis; therefore, of the studies including an Ad26.RSV.preF-based regimen mentioned in Section 2.2, 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 toward an increase in the frequency of some local AEs with an increase in Ad26 dose, ie, injection site pain (18.7% of participants at the 0.8×10^{10} vp dose level, 38.7% of participants at the 2×10^{10} vp dose level, 52.0% of participants at the 5×10^{10} vp dose level, and 77.1% of participants at the 1×10^{11} vp dose level), and to a lesser extent injection site swelling (6.7%, 2.7%, 9.3%, and 17.6%, respectively). Injection site warmth was not collected at the 0.8×10^{10} vp and the 2×10^{10} vp dose level. The frequency of injection site warmth at the 5×10^{10} vp and the 1×10^{11} vp dose level was 19.5%, and 26.7%, respectively. This trend needs to be interpreted with caution since the participants in the lower dose groups (0.8×10^{10} vp and 2×10^{10} vp dose level) were all from a single study (VAC52150EBL3002), and the majority of the participants in the highest dose group (1×10^{11} vp dose level) were also from a single study (VAC18193RSV2003).

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

Solicited systemic AEs reported in ≥10% of children aged 1-3 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 toward an increase in the frequency of solicited systemic AEs with an increase in Ad26 dose (35.3% at the 0.8×10^{10} vp dose level, 49.3% at the 2×10^{10} vp dose level, 64.5% at the 5×10^{10} vp dose level, and 70.4% at the 1×10^{11} vp dose level). The frequency of severe solicited

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

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

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

General Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine and/or 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 6.9.

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 or suspected allergy, or history of anaphylaxis, or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine) will be excluded from the study.

[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.

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

Pregnancy and Birth Control

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

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

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 vaccination (See Section 5.1, Inclusion Criteria). Women who are pregnant or breastfeeding will be excluded from the study. Women who become pregnant while enrolled in the study will not receive further study vaccine but may continue other study procedures at the discretion of the investigator (see Section 7.1, Discontinuation of Study Vaccination).

Risks from Blood Draws

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

Risks from Collection of Nasal Swabs

Collection of a nasal swab may cause a nosebleed.

Theoretical Risk of Enhanced Disease

Vaccine-associated enhanced disease has been described for SARS-CoV and MERS-CoV in some animal models,[0,0,0,0,0] 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, Background). Participants in the present study will be informed of the theoretical risk of disease enhancement in the ICF. Furthermore, as a risk mitigation strategy, all participants in the study will be passively and actively monitored for acquisition of molecularly confirmed COVID-19 (see Section 4.1, Section 8.1.2, and Section 10.8). This active and passive surveillance system for detection of COVID-19 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 VAC31518COV2001 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 immediately inform the SMC 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 SMC will be described in the Statistical Analysis Plan (SAP).

Unknown Risks

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

2.3.2 Benefits of Study Participation

Participants may benefit from clinical testing and physical examination.

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

2.3.3 Benefit-Risk Assessment of Study Participation

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

- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5, Study Population) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:

  In general, safety evaluations will be performed at scheduled visits during the study, as indicated in the Schedule of Activities.

  After each vaccination, participants will remain at the study site for at least 1 hour and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a diary to document solicited signs and symptoms. Details are provided in Section 8.2, Safety Assessments and Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting.

  The investigator or the designee will document unsolicited AEs as indicated in Section 8.2, Safety Assessments, Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.4.

From the time of local approval of protocol Amendment 5 onwards, TTS is considered to be an AESI (Section 8.3.6). Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/μL[0]]) 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.

- 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 hematology laboratory assessments (see Section 10.2) will be performed for adults as indicated in the SoA (see Section 1.3).

  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 SMC reviews all safety data (see Section 10.3.6).

  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.

  For the adolescent cohort, an SMC will review safety data of sentinels before proceeding to enrollment of the full cohort (as detailed in Section 4.1).

3. OBJECTIVES AND ENDPOINTS

ADULTS

Objectives	Endpoints
Primary	
• To assess the humoral immune response to 3 dose levels ($5x10^{10}$ virus particle (vp), $2.5x10^{10}$ vp, $1.25x10^{10}$ vp) of Ad26.COV2.S, administered intramuscularly (IM) as a 2-dose schedule at a 56-day interval, 28 days after Vaccination 2.	• Serological response to vaccination as measured by virus neutralization assay (VNA) titers and enzyme-linked immunosorbent assay (S-ELISA, ELISA Units/mL [EU/mL]), 28 days after Vaccination 2. • Antibody geometric mean titers (GMTs) (VNA) and geometric mean concentrations (GMCs) (S-ELISA), 28 days after Vaccination 2.
• To assess the humoral immune response to 2 dose levels ($1 x10^{11}$ vp and $5x10^{10}$ vp) of Ad26.COV2.S, administered IM as a single vaccination, 28 days after Vaccination 1.	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 28 days after Vaccination 1. • Antibody GMTs (VNA) and GMCs (S-ELISA), 28 days after Vaccination 1.

Objectives	Endpoints
• To assess the humoral immune response to Ad26.COV2.S at the $5x10^{10}$ vp dose level, administered IM as a 2-dose schedule at a 28-day and at an 84-day interval, 28 days after Vaccination 2.	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 28 days after Vaccination 2. • Antibody GMTs (VNA) and GMCs (S-ELISA), 28 days after Vaccination 2.
• To assess the safety and reactogenicity of Ad26.COV2.S, administered IM at several dose levels, as a 2-dose or a single-dose schedule.	• Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • Unsolicited AEs for 28 days after each vaccination. • Serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study (from first vaccination until end of the study).
Secondary	
• To assess the anamnestic response to antigen presentation of Ad26.COV2.S at the $1.25x10^{10}$ vp dose level, administered 4 months after Vaccination 2 (2-dose schedule) or 6 months after a Vaccination 1 (single-dose schedule), 7 days after antigen presentation (Groups 1-5, 7 and 9).	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 7 days after antigen presentation. • Antibody GMTs (VNA) and GMCs (S-ELISA), 7 days after antigen presentation.
• To assess the safety and reactogenicity of antigen presentation of Ad26.COV2.S at the $1.25x10^{10}$ vp dose level, administered 4 months after Vaccination 2 (2-dose schedule) or 6 months after a Vaccination 1 (single-dose schedule) (Groups 1-5, 7 and 9).	• Solicited local and systemic AEs for 7 days after antigen presentation. • Unsolicited AEs for 28 days after antigen presentation. • SAEs and AESIs throughout the study (from antigen presentation until end of the study).
• To assess the humoral immune response to Ad26.COV2.S across all groups, at all blood collection timepoints.	• Neutralizing antibody titers to the wild-type SARS-CoV-2 virus expressing S protein as measured by VNA, at all blood collection timepoints. • Binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA, at all blood collection timepoints.

Objectives	Endpoints
Exploratory	
• To assess the cellular immune response to Ad26.COV2.S at different dose levels in a subset of participants (Groups 1 to 6) at selected blood collection timepoints.	• 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 (PBMC) and intracellular staining (ICS) including cluster of differentiation (CD) 4^+/$CD8^+$, interferon gamma (IFNγ), interleukin (IL)-2, tumor necrosis factor alpha (TNFα), IL-4, IL-5, IL-13, and/or other Th1/Th2 markers.
• To further assess the humoral immune response to Ad26.COV2.S.	• 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). • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype. • Passive transfer: analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. • Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants. • Adenovirus neutralization as measured by VNA.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms.	• The number of participants with molecularly confirmed COVID-19. • Presence and severity of COVID-19 signs and symptoms as measured by Symptoms of Infection with Coronavirus-19 (SIC).
• To examine the immune response in vaccinated individuals after natural SARS-CoV-2 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 pseudovirions expressing S protein). • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein. • Analysis of gene expression by ribonucleic acid (RNA) transcript profiling.

Objectives	Endpoints
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of asymptomatic participants with positive non-S protein ELISA (eg, nucleocapsid [N] protein ELISA), as feasible. • The number of asymptomatic participants with a SARS-CoV-2 positive RT-PCR test.
• To assess hematology laboratory parameters after Ad26.COV2.S administration.	• Lupus anticoagulants, anti-β2 glycoprotein, anti-cardiolipin, D-dimers, anti-PF4.
• To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints.

ADOLESCENTS[a]

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of a single dose of Ad26.COV2.S, administered IM at the $2.5x10^{10}$ vp dose level.	• Solicited local and systemic AEs for 7 days after vaccination. • Unsolicited AEs for 28 days after vaccination. • SAEs (incl. Multisystem Inflammatory Syndrome in Children [MIS-C]) and AESIs throughout the study (from first vaccination until end of the study).
Secondary	
• To assess the humoral immune response to a single dose of Ad26.COV2.S at the $2.5x10^{10}$ vp dose level, administered IM.	• Serological response to vaccination as measured by VNA titers and ELISA (S-ELISA, EU/mL), 28 days after vaccination. • Antibody GMTs (VNA) and GMCs (S-ELISA), 28 days after vaccination.
• To assess the humoral immune response to Ad26.COV2.S at the $2.5x10^{10}$ vp dose level, at all blood collection timepoints.	• Neutralizing antibody titers to the wild-type SARS-CoV-2 virus expressing S protein as measured by VNA, at all blood collection timepoints. • Binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA, at all blood collection timepoints.

[a] Not applicable in Germany and the Netherlands

Objectives	Endpoints
Exploratory	
• To further assess the humoral immune response to Ad26.COV2.S.	• 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). • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype. • Passive transfer: analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. • Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants. • Adenovirus neutralization as measured by VNA.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms.	• The number of participants with molecularly confirmed COVID-19. • Presence and severity of COVID-19 signs and symptoms as measured by Symptoms of Infection with Coronavirus-19 (SIC).
• To examine the immune response in vaccinated individuals after natural SARS-CoV-2 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 pseudovirions expressing S protein). • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein. • Analysis of gene expression by ribonucleic acid (RNA) transcript profiling.
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of asymptomatic participants with positive non-S protein ELISA (eg, nucleocapsid [N] protein ELISA), as feasible. • The number of asymptomatic participants with a SARS-CoV-2 positive RT-PCR test.
• To assess coagulation-related parameters at selected blood sample collection timepoints.	• platelet factor 4-heparin complex (anti-PF4) antibodies.

HYPOTHESIS

No formal hypothesis testing will be performed in this study.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adolescents aged 12 to 17 years, inclusive, adults aged 18 to 55 years inclusive, and adults in good or stable health aged 65 years and older. Countries may participate in the adult and adolescent portions of the study or they may participate in either the adult or adolescent portion.

In adults, the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in 1- and 2-dose vaccination regimens followed by antigen presentation after 4 months (2-dose regimen) or 6 months (single-dose regimen), will be evaluated across a range of dose levels and vaccination intervals. At the start of this study for adults, interim safety data through Day 29 and interim immunogenicity data, including VNA and ELISA through Day 29 and Day 15 Th1/Th2 response, from Cohort 1a of the first-in-human study VAC31518COV1001 in adults will be available.

In adolescents, the safety, reactogenicity, and immunogenicity of a single dose of Ad26.COV2.S will be evaluated.

Participants will receive Ad26.COV2.S or a placebo. In adults, 4 dose levels of Ad26.COV2.S will be administered IM: $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp. Adolescents will be administered $2.5x10^{10}$ vp.

With the implementation of protocol Amendment 5, enrolled adult participants will be unblinded and those who initially received placebo in the primary vaccine regimen will be offered 2 doses of the Ad26.COV2.S vaccine at 5×10^{10} vp (adult Groups 6, 8 and 10).

ADULTS

A target of approximately 550 adult participants will initially be enrolled in this study in a blinded manner and randomly assigned to 1 of 10 groups to receive 1- or 2-doses of active Ad26.COV2.S vaccine or placebo at a dose of $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp, or $1.25x10^{10}$ vp and at a 28-day, 56-day or 84-day interval.

A single antigen presentation injection with $1.25x10^{10}$ vp Ad26.COV2.S (Groups 1-5, 7, 9) or placebo (Groups 6, 8, 10) will be administered 4 months after the second vaccination (ie, 4 months post-vaccination 2 in the 2-dose regimens and 6 months after Vaccination 1 in the 1-dose regimens).

After each vaccination, all participants will remain under observation at the study site for at least 1 hour to monitor for the presence of any acute reactions and solicited events.

With implementation of protocol Amendment 5, participants who were initially enrolled to receive placebo (Groups 6, 8 and 10), will be offered a 2-dose (28-day interval) Ad26.COV2.S vaccination regimen at the $5x10^{10}$ vp dose level. In October 2020, the study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2 (Visit 4), rendering the

intent of the 28-day vaccination interval in these groups futile. The goal in offering 2 doses of study vaccine to those participants who initially received placebo in this study is to recreate this 28-day vaccination interval, and to restore the objectives associated with this interval. The original 28-day interval target group was 75 participants. Hence the total number of placebo recipients from Groups 6, 8 and 10 (target n 75) is intended to fulfill the original target enrollment for Group 7.

With implementation of protocol Amendment 5, all adult participants will be unblinded to the primary vaccination regimen, and, adults who received placebo in the primary vaccine regimen, will receive a 2 dose active Ad26.COV2.S vaccine regimen at a 28-day interval and at a dose level of $5x10^{10}$ vp, in an open-label manner. Per group, approximately one third of participants will be 65 years and older.

Adult participants who received the active vaccine in the primary vaccine regimen will be followed up for 12 months after vaccination 2; adult participants who received placebo in the primary vaccine regimen will be followed up for 6 months after receipt of the unblinded vaccination 1 (ie, receipt of the first active vaccine following unblinding).

Groups 1-6

400 participants (75 participants per active vaccine group, 25 in the placebo group) will be randomized in parallel in a 3:3:3:3:3:1 ratio to 1 of 6 vaccination groups. Participants will receive a 2-dose (56-day interval, Groups 1-3) vaccination regimen at different dose levels (5×10^{10} vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) or single-dose vaccination regimen (Groups 4-5) at different dose levels (1×10^{11} vp, $5x10^{10}$ vp), or placebo (Group 6). For blinding purposes, participants in the single-dose groups (Groups 4-5) will receive a placebo vaccination on Day 57. Additional exploratory cellular immunogenicity evaluations (PBMC) will be performed in a subset of participants (21/group in Groups 1-5, 7 in Group 6; at selected sites). Participants in Group 6 who received 2-doses of placebo in the primary vaccine regimen will receive 2 doses of active vaccine at a single dose level of $5x10^{10}$ vp, at a 28-day interval.

Groups 7-8

75 participants (50 participants in the active vaccine group, 25 in the placebo group) will be randomized in parallel in a 2:1 ratio, to 1 of 2 vaccination groups. Participants will receive a 2 dose (28-day interval, Groups 7[a]) vaccination regimen at a 5×10^{10} vp dose level or placebo (Group 8). Participants in Group 8 who received 2-doses of placebo in the primary vaccine regimen will receive 2 doses of active vaccine at a single dose level of $5x10^{10}$ vp, at a 28-day interval.

[a] Group 7 and 8: only 2 subjects (one in each group) are vaccinated at a 28-day interval, due to a study pause

Groups 9-10

75 participants (50 participants in the active vaccine group, 25 in the placebo group) will be randomized in parallel in a 2:1 ratio, to 1 of 2 vaccination groups. Participants will receive a 2 dose (84-day interval, Group 9) vaccination regimen at a 5×10^{10} vp dose level or placebo (Group 10). Participants in Group 10 who received 2-doses of placebo in the primary vaccine regimen will receive 2 doses of active vaccine at a single dose level of $5x10^{10}$ vp, at a 28-day interval.

The vaccination schedules are presented in Table 2.

Table 2: Vaccination Schedules Adults

Adults ≥18 to ≤55 Years and ≥65 Years

Group	N	**Day 1 (Vaccination 1)** Ad26.COV2.S dose level / placebo	**Day 29 (Vaccination 2)** Ad26.COV2.S dose level / placebo	**Day 57 (Vaccination 2)** Ad26.COV2.S dose level / placebo	**Day 85 (Vaccination 2)** Ad26.COV2.S dose level / placebo	**4 Months Post-Vaccination 2 (Injection 3)**[1] Ad26.COV2.S dose level/ placebo	**Unblinded Vaccination 1** Ad26.COV2.S dose level	**Day 29 Post Unblinded Vaccination 1 (Unblinded Vaccination 2)** Ad26.COV2.S dose level
1	75	**5**x10^{10} vp		**5**x10^{10} vp		**1.25**x10^{10} vp	-	-
2	75	**2.5**x10^{10} vp		**2.5**x10^{10} vp		**1.25**x10^{10} vp	-	-
3	75	**1.25**x10^{10} vp		**1.25**x10^{10} vp		**1.25**x10^{10} vp	-	-
4	75	**1**x10^{11} vp		Placebo		**1.25**x10^{10} vp[2]	-	-
5	75	**5**x10^{10} vp		Placebo		**1.25**x10^{10} vp[2]	-	-
6	25	Placebo		Placebo		Placebo	**5**x10^{10} vp	**5**x10^{10} vp
7	50	**5**x10^{10} vp	**5**x10^{10} vp			**1.25**x10^{10} vp	-	-
8	25	Placebo	Placebo			Placebo	**5**x10^{10} vp	**5**x10^{10} vp
9	50	**5**x10^{10} vp			**5**x10^{10} vp	**1.25**x10^{10} vp	-	-
10	25	Placebo			Placebo	Placebo	**5**x10^{10} vp	**5**x10^{10} vp

N number of participants; vp virus particles.

1. Antigen presentation
2. 6 Months after Vaccination 1 in the single dose regimens (Groups 4 and 5).

ADOLESCENTS[a]

From the time of protocol Amendment 2, adolescent participants (12 to 17 years of age, inclusive) were to be enrolled in a randomized and staggered manner.

The safety profile of Ad26.COV2.S in adolescents was planned to be assessed separately by age group and by escalating dose, with the 2 adolescent age groups (12 to 15 years and 16 to 17 years) assessed independently and enrollment progressing in a sequential manner. The safety and tolerability of the Ad26.COV2.S vaccine was to be assessed in the first instance in a group of sentinels at Day 4 post-vaccination, and if acceptable, in the larger safety cohort at Day 8 post-vaccination. The Day 4 and Day 8 post-vaccination safety profiles of the Ad26.COV2.S vaccine at the $2.5x10^{10}$ vp dose level in the sentinel and safety cohorts was to be assessed in participants at 16 to 17 years of age, by the Safety Monitoring Committee (SMC) before progressing to enrollment of the sentinel group of participants at 12 to 15 years of age (see Figure 7).

The first doses of Ad26.COV2.S study vaccine at $2.5x10^{10}$ vp were to be administered to a sentinel group of 11 participants in Groups A-C (randomly assigned at a ratio of 5:5:1 to Ad26.COV2.S, with 5 each from Groups A and B, and 1 participant in Group C to receive placebo), to monitor for any unexpected severe adverse reactions. The sentinel participants were to be vaccinated at least 1 hour apart even if enrolled at different study sites. A telephone call was to be made to each of these 11 sentinel participants on Day 4 post-vaccination to collect safety data, which was to include solicited and unsolicited AEs and SAEs. The collected data were to be reviewed in a blinded manner by the principal investigator (PI) and the sponsor's study responsible physician/scientist (SRP/S). Randomization and vaccination of additional participants were to be halted until the review is completed. The SMC was to review the unblinded Day 4 post-vaccination safety data, including solicited and unsolicited AEs and SAEs, and if the safety profile was found to be acceptable, a safety cohort of 22 participants in Groups A-C (randomly assigned at a ratio of 5:5:1 to Ad26.COV2.S, with 10 each from Groups A and B, and 2 participants in Group C to receive placebo) was to be enrolled. The Day 8 post-vaccination safety data from both sentinel groups, including solicited and unsolicited AEs and SAEs, was also to be reviewed by the SMC, and in the absence of any safety concerns, the enrollment and vaccination of the remainder of the participants for Groups A-C (49 participants) in this age group can proceed, and simultaneously, sentinel enrollment in Groups D-F (to receive Ad26.COV2.S study vaccine at $5x10^{10}$ vp) was to start. In addition, enrollment of the younger age group of adolescents (12-15 years, inclusive) was to proceed for Groups A-C.

After vaccination, all participants were to remain under observation at the study site for at least 1 hour (including participants in the Sentinel and Safety Cohort) to monitor for the presence of any acute reactions and solicited events.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16-17 year old age group at a dose of $2.5x10^{10}$ vp enrolled in this study, the entire COVID-19 vaccine program was paused to evaluate a safety concern of TTS in adults. During this pause, the

[a] Not applicable in Germany and the Netherlands

safety and immunogenicity data for these 33 adolescent participants was evaluated (see current version of Investigator's Brochure[0]). While the IDMC endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level, the sponsor has decided not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose in Study VAC31518COV2001 and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12-17 years of age, and no further enrollment of this age group will take place in this study.

Therefore, per protocol Amendment 6, the 33 adolescents already enrolled at the time of Amendment 6 will continue to be followed in this study in accordance with the planned Schedule of Activities (Sections 1.3.5 and 1.3.6), but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at $2.5x10^{10}$ vp.

With the implementation of Amendment 6, the 33 adolescent participants will be unblinded to the primary vaccination regimen. At this time, adolescents who received placebo (Group C) will receive a single dose of Ad26.COV2.S at the 2.5 $x10^{10}$ vp dose level in an open-label manner.

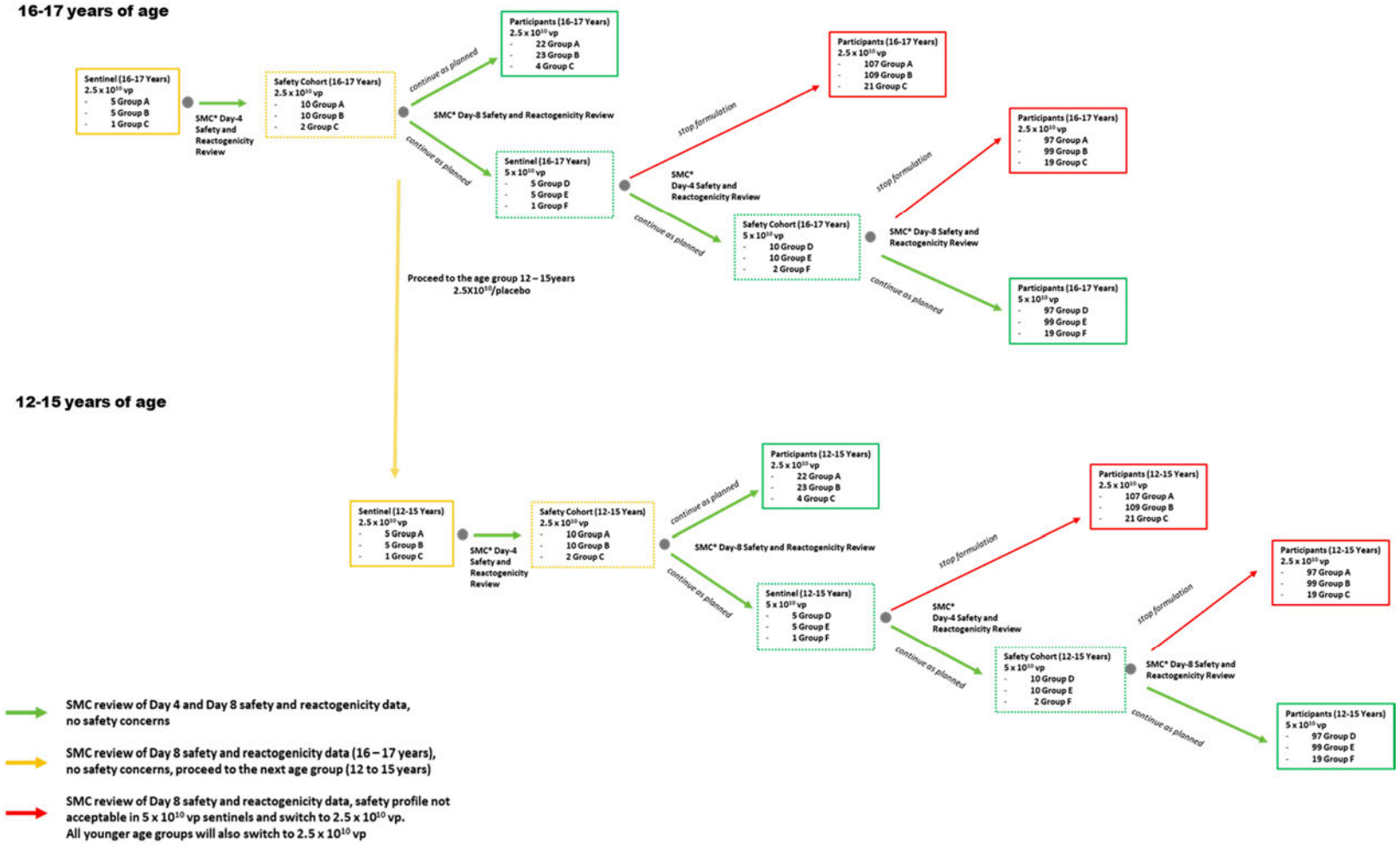
Table 3: Vaccination Schedules – Adolescents

Adolescents: 12 to 17 Years of Age, Inclusive

Group	**Day 1 (Vaccination 1)** Ad26.COV2.S dose level or placebo	**With Implementation of Amendment 6 (At approximately 6 Months of Study Participation) (Unblinded Vaccination 1)** Ad26.COV2.S dose level
A	**2.5**$x10^{10}$ vp	-
B	**2.5**$x10^{10}$ vp	-
C	Placebo	**2.5**$x10^{10}$ vp

vp virus particles

Figure 7: Sentinel Decision Tree for Staggered Enrollment in Groups A-F – Adolescents



* For more information on the SMC, see Section 10.3.6.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16 17 year old age group at a dose of $2.5x10^{10}$ vp enrolled in this study, the entire Ad26.COV2.S COVID 19 vaccine program was paused to evaluate a safety concern of TTS in adults. During this pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated. While the IDMC endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level, the sponsor has decided not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12 17 years of age, and no further enrollment of this age group will take place in this study.

Therefore, per protocol Amendment 6, the 33 adolescents already enrolled at the time of Amendment 6 will continue to be followed in this study in accordance with the planned Schedule of Activities, but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at $2.5x10^{10}$ vp.

Study Duration

The study duration from screening until the last follow-up visit will be approximately 15 months for adult participants in Groups 1-5, approximately 14 months for adult participants in Group 7, and approximately 16 months for adult participants in Group 9. The study duration for adult participants in Groups 6, 8 and 10 is approximately 15 months. For the majority of participants in Group 7, whose vaccination 2 was delayed due to the study pause, study duration will be approximately 15 months. For adults, the study will consist of a 28-day screening phase, a 1 to 3-month vaccination phase depending on the vaccination interval and a 12-month follow-up (which includes an antigen presentation 4 months after vaccination 2).

The study duration from screening until the last follow-up visit will be approximately 13 months per adolescent participant in Groups A-C.

If a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted. The end of study is considered as the last visit for the last participant in the study.

Study Procedures

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

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

The reporting periods of AEs, SAEs, and special reporting situations are detailed in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting. Reporting periods for concomitant therapy are outlined in Section 6.9, Prestudy and Concomitant Therapy.

A final safety follow-up visit is foreseen 12 months after Vaccination 2 (adults) and 12 months after Vaccination 1 (adolescents).

For the assessment of COVID-19, and to assess possible ERD, participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms, and for documentation of body temperature and pulse oximetry results. Baseline pulse oximetry will be conducted at Visit 1. If a participant meets the prespecified criteria for (suspected)

COVID-19[15] (as detailed in Section 8.1.2.1), procedures should be followed as detailed in Section 8.1.2.

The occurrence of asymptomatic SARS-CoV-2 infection will be assessed by a non-S-protein ELISA (eg, SARS-CoV-2 N-ELISA), as feasible (see Section 8.1.3, Asymptomatic SARS-CoV-2 Infection) and by collection of positive RT-PCR results for SARS-CoV-2, regardless where the testing was performed (under the auspices of the study or through a private or public laboratory independent of the study).

From all participants, blood samples will be collected at selected timepoints indicated in Section 1.3, Schedule of Activities for humoral immunogenicity assessments, with an emphasis on neutralizing and binding antibody responses. In a subset of adult participants (approximately 112; 21 participants per group in Groups 1-5, 7 participants in Group 6; at selected sites), cellular immunogenicity (PBMC) will be assessed at selected timepoints. Further details about the immunogenicity assessments are provided in Section 8.1.1.

Initially, an internal DRC was commissioned for this study. However, an independent IDMC was installed to include VAC31518COV2001 on 29 October 2020, and the IDMC kickoff for review was held on 15 December 2020. In light of the transition of DRC to IDMC, when the term SMC is mentioned, it can refer to either. Refer to Section 10.3.6 for details.

The planned interim, primary, and final analyses are detailed in Section 9.5, Planned Analysis.

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

4.2. Scientific Rationale for Study Design

Dose Level Selection

The rationale behind the selection of the dose levels 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.

[15] 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.

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

Biomarker Collection

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

4.2.1. Study-Specific Ethical Design Considerations

Potential participants and their legal guardians (for adolescents as appropriate) will be fully informed of the risks and requirements of the study and, during the study, they will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent 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. Potential participants will only be enrolled if participants, and their legal guardians (as appropriate for adolescents) are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent/assent voluntarily.

The primary ethical concern is that this study will be performed in adult and adolescent 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. The potential risk to adolescent participants in this study include study vaccine exposure, with the potential for AEs. See Section 4.3 for the justification for dose level to be used in adolescents. 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.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian(s) of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent should be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the local regulations and practice. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected from adults 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,[0,0] as well as the European Commission guidelines of 500 mL per donation and 3 L per consecutive 12 month period.[0]

The total blood volume to be collected from adolescents is considered acceptable according to guidelines[0,0,0] and will not exceed 40 mL per blood draw or 120 mL over a 30-day period.

4.3. Justification for Dose

Adults

The regimen and dose selection in this study are aimed at providing information on safety and immunogenicity of multiple 2-dose and single-dose schedules of the Ad26.COV2.S vaccine, including lower dose levels (ie, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) compared to the dose levels used in the first-in-human study (VAC31518COV1001). In October 2020, the study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2 (Visit 4), rendering the intent of the 28-day vaccination interval in these groups futile. The goal in offering 2 doses of study vaccine to those participants who initially received placebo in this study is to recreate this 28-day vaccination interval, and to restore the objectives associated with this interval. The original 28-day interval target group was 75 participants. Hence the total number of placebo recipients from Groups 6, 8 and 10 (target n 75) is intended to fulfill the original target enrollment for Group 7.

Four dose levels will be evaluated: $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp.

- The evaluation of the $2.5x10^{10}$ vp vaccine dose level will provide insight (immunogenicity) in the possibility to use this dose level for dose sparing.

- The evaluation of the $1.25x10^{10}$ vp vaccine dose level will allow for the assessment of immunogenicity of this dose level which is representative of the vaccine titer of the $5x10^{10}$ vp dose level at the end of the foreseen shelf-life in the context of emergency use with storage at 2-8 °C.

By lowering the dose level (ie, to $2.5x10^{10}$ vp and $1.25x10^{10}$ vp), there will also be a potential to immunobridge to a lower dose level regimen, should the efficacy study (VAC31518COV3001) provide evidence of an immune correlate of protection.

The regimen is selected based on previous preclinical and clinical data from other Ad26-based vaccines.

Note that 2 clinical studies, VAC52150EBL3002 (Ebola) and IPCAVD001 (HIV), showed that Ad26-based vaccines induce a potent humoral and cellular immune response at doses equivalent or lower than $1.25x10^{10}$ vp.

Adolescents

Available platform data, as well as safety data from the VAC31518COV1001 study, (see Section 2.2 and Section 2.3.1) supported initiating evaluation of Ad26.COV2.S in adolescents aged 12 to 17 years, inclusive, with the dose levels as proposed. From the time of protocol Amendment 2, in Groups A-F, 2 dose levels were to be evaluated: $2.5x10^{10}$ vp and $5x10^{10}$ vp.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16 17 year old age group at a dose of $2.5x10^{10}$ vp enrolled in this study, the entire Ad26.COV2.S COVID 19 vaccine program was paused to evaluate a safety concern of thrombosis with TTS in adults. During this pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated. While the IDMC endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level, the sponsor has decided not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12-17 years of age, and no further enrollment of this age group will take place in this study.

Therefore, per protocol Amendment 6, the 33 adolescents already enrolled at the time of Amendment 6 will continue to be followed in this study in accordance with the planned Schedule of Activities, but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at $2.5x10^{10}$ vp.

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 each participating study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

An adult participant will be considered to have completed the study if he or she has completed assessments at the 12-month post vaccination 2 visit (on Day 393 for Groups 1-5, Day 365 for Group 7, and Day 421 for Group 9) or the 6-month post unblinded vaccination 1 visit for Groups 6, 8 and 10.

An adolescent participant will be considered to have completed the study if he or she has completed assessments at the 12-month post vaccination 1 visit (Groups A and B) or 6 month post active vaccination visit (Group C).

Participants who prematurely discontinue study vaccination for any reason before that time will not be considered to have completed the study.

5. STUDY POPULATION

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

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

NOTE: Investigators should ensure that all study enrollment criteria have been met prior to the first vaccination. 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 described in Section 10.3.

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria for Adults (18-55 Years, Inclusive and 65 Years or Older)

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

1 Participant must sign an ICF indicating that he or she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.

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

3 Participant is 18 to 55 years of age, inclusive, or 65 years of age or older on the day of signing the ICF.

4 Participant must have a body mass index (BMI) <30.0 kg/m^2.

5 Criterion modified per Amendment 1:

5.1. Participant 18 to 55 years of age, inclusive: participant must be healthy, in the investigator's clinical judgment, as confirmed by medical history, physical examination, and vital signs performed at screening, and must not have comorbidities related to an increased risk of severe COVID-19, except for smoking, which is allowed (see also exclusion criterion 21).

Participant 65 years of age and older: in the investigator's clinical judgment, participant must be either in good or stable health. Participant may have underlying

illnesses, as long as the symptoms and signs are medically controlled and not considered to be comorbidities related to an increased risk of severe COVID-19[16], except for smoking, which is allowed (see also exclusion criterion 21). If 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. Participant will be included on the basis of physical examination, medical history, and vital signs[17].

6 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 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

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

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

2. intrauterine device (IUD)

3. intrauterine hormone-releasing system (IUS)

4. bilateral tubal occlusion/litigation procedure

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

6. sexual abstinence*

Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from signing the informed consent until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in*

[16] Participants may have hypertension of mild severity, 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).

[17] 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.

relation to the duration of the study and the preferred and usual lifestyle of the participant.

7 All participants of childbearing potential must:

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

   b. Have a negative highly sensitive urine pregnancy test 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.

5.1.2. Inclusion Criteria for Adolescents (12-17 Years, Inclusive)

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

1 Participants must have signed an ICF (or their legally acceptable representative or parent(s) [preferably both parents if available or as per local requirements] must sign) indicating that they understand the purpose of, and procedures required for, the study, are willing/able to adhere to the prohibitions and restrictions specified in the protocol and study procedures, and are willing (or the parents are willing for their adolescent) to participate in the study. Informed assent must be obtained from adolescents, depending on local regulations and practice.

2 Participants who have given written consent or assent as required by local regulations after the nature of the study has been explained to them according to local regulatory requirements.

3 Participant is 12 to 17 years of age, inclusive, on the day of signing the ICF

4 Participant must be healthy, in the investigator's clinical judgment, as confirmed by medical history, physical examination, and vital signs performed at screening, and must not have comorbidities related to an increased risk of severe COVID-19, as listed in Section 10.10, summarized from the CDC website available at the time of writing this protocol amendment 2.

5 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):

   a. Not of childbearing potential

   b. Of childbearing potential and practicing a highly effective method of contraception and agrees to remain on such a method of contraception from signing the informed consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. The investigator should evaluate the potential

for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first vaccination. Highly effective methods for this study include:

1. hormonal contraception

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

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

2. intrauterine device (IUD)

3. intrauterine hormone-releasing system (IUS)

4. bilateral tubal occlusion/litigation procedure

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

6. sexual abstinence*

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

6 All participants of childbearing potential must:

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

b. Have a negative highly sensitive urine pregnancy test immediately prior to each study vaccine administration.

Note: If the pregnancy test result is positive, in order to maintain participant confidentiality, the investigator will ensure adequate counseling and follow-up will be made available.

7 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.

8 Participant and, where required by local regulation, parent(s)/legal guardian(s) are available and willing to participate for the duration of the study visits and follow-up.

9 Participant and, where required by local regulation, parent(s)/legal guardian(s) must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for Adults (18-55 years, Inclusive and 65 Years or Older)

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 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[0]).

4 Criterion modified per Amendment 3

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

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

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

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

7 Participant received treatment with immunoglobulins 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:

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

d. 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 2:

9.2 Criterion modified per Amendment 3:

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 19) and during the study except under the conditions described in Section 6.7.

10 Criterion modified per Amendment 1:

10.1 Participant is a woman who is pregnant, breastfeeding, or planning to become pregnant within 3 months after the last dose of study vaccine.

11 Participant has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

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

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

14 Criterion Deleted per Amendment 4.

14.1 Criterion reinstated per Amendment 5:

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 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.

17 Participant cannot communicate reliably with the investigator.

18 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.

19 Participant previously received a coronavirus vaccine.

20 Participant has a positive diagnostic test result for past (serological testing) or current (PCR based viral RNA detection) SARS-CoV-2 infection at screening.

21 Criterion modified per Amendment 1:

21.1 Criterion modified per Amendment 3:

21.2 Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19, 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 $\geq$ 30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; and sleep apnea. This list is consistent with the list of conditions that increase the risk of progression to severe COVID-19 available at the CDC website at the time of writing of this protocol[0], except for smoking, which is allowed. The data from the CDC website is summarized in Section 10.9.

Applicable only to participants 65 years of age and older: Participants may have hypertension of mild severity 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).

22 Participant who is currently working in an occupation with a high risk of exposure to SARS-CoV-2 infection (eg, health care worker or emergency response personnel who work in close contact with SARS-CoV-2 infected patients) or considered at the investigator's discretion to be at increased risk to acquire COVID-19 for any other reason

23 Participant who has had a known exposure to an individual with confirmed COVID-19 or SARS-CoV-2 infection within the past 2 weeks

24 History of confirmed SARS or MERS.

5.2.2. Exclusion Criteria for Adolescents (12-17 Years, Inclusive)

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.

3 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[0]).

4 Participants who required chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the study vaccination. (For corticosteroids, this means prednisone, or equivalent, ≥ 20mg/day. Inhaled and topical steroids are allowed). For participants below 45 kg, the dose is 1 mg/kg/day.

Participants in treatment with systemic corticosteroids given p.o., i.v., i.m. ≤ 1 month prior to inclusion or during the study. Participants administered corticosteroid topically or by asthma inhalators are eligible for inclusion

5 Participants with a history of illness or with an ongoing illness that, in the opinion of the investigator, may pose additional risk to the participant if he/she participates in the study

6 Any serious, chronic, or progressive disease (eg, neoplasm, diabetes, cardiac disease, hepatic disease, progressive neurological disease or seizure disorder; autoimmune disease, HIV infection or AIDS, blood dyscrasias, bleeding diathesis, signs of cardiac or renal failure, or severe malnutrition)

7 Participant has obesity (as defined by the Growth Chart being used as appropriate in the participant's country, e.g. the CDC Growth Chart)[0]

8 Participant received treatment with immunoglobulins 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.

9 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.

10 Criterion modified per Amendment 1:

10.1 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 against SARS-CoV-2 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 17) and during *the study except under the conditions described in Section 6.7*.

11 Participant is pregnant, breastfeeding, or planning to become pregnant within 3 months after the last dose of study vaccine.

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

13 Criterion Deleted per Amendment 4.

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

15 Criterion Modified per Amendment 4:

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

16 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.

17 Participant previously received a coronavirus vaccine.

18 Participant has a positive diagnostic test result for past (serological testing) or current (PCR based viral RNA detection) SARS-CoV-2 infection at screening.

19 Participant who has had a known exposure to a person with confirmed COVID-19 or SARS-CoV-2 infection within the past 2 weeks

20 History of confirmed SARS or MERS.

21 Criterion Added per Amendment 4

Participant has a history of Kawasaki disease.

22 Criterion Added per Amendment 4

Participant has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator,

participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

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 6.9, 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 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/assent process, and then restart a new screening phase.

5.5. Criteria for Temporarily Delaying Administration of Study Vaccination

The following events constitute a temporary contraindication to study vaccination:

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature ≥38.0°C [100.4°F]) within 24 hours prior to the planned time of vaccination.

If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for one of the subsequent

vaccinations, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in Section 8, Study Assessments and Procedures).

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

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1. Study Vaccinations Administered

Ad26.COV2.S (also known as Ad26COVS1) will be supplied at a concentration of $1x10^{11}$ vp/mL and $2x10^{11}$ vp/mL as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer will be supplied as diluent 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 will be supplied as a 0.9% NaCl solution.

Adult participants in Groups 1-6 will be vaccinated on Day 1 and Day 57, in Groups 7-8 on Day 1 and Day 29, in Groups 9-10 on Day 1 and Day 85.

Adolescent participants in Groups A-B will be vaccinated with a single dose of Ad26.OV2.S at $2.5x10^{10}$ vp on Day 1. Adolescent participants in Group C who received placebo on Day 1 will receive a single dose of Ad26.OV2.S at $2.5x10^{10}$ vp following unblinding at approximately 6 months of study participation.

A volume of 0.5 mL will be administered to all (adult and adolescent) participants.

- Ad26.COV2.S:

  $1x10^{11}$ vp dose level (Adult Group 4): 0.5 mL is withdrawn from one vial containing 0.75mL $2x10^{11}$ vp/mL.

  $5x10^{10}$ vp dose level (Adult Groups 1, 5, 7, 9): 0.5 mL is withdrawn from one vial containing 0.75 mL $1x10^{11}$ vp/mL.

  $2.5x10^{10}$ vp dose level (Adult Group 2, and Adolescent Groups A, B and C): 0.75 mL of formulation buffer is added to a vial containing 0.75 mL $1x10^{11}$ vp/mL, providing $5x10^{10}$ vp/mL in a vial with an extractable volume of more than 1 mL. Then 0.5 mL will be withdrawn from this vial.

  $1.25x10^{10}$ vp dose level (Adult Group 3 and antigen presentation in Groups 1-5, 7 and 9): 0.4 mL is withdrawn from one vial containing 0.75 mL 1×10^{11} vp/mL and added to a vial containing 1.2 mL formulation buffer, providing 2.5×10^{10} vp/mL in a vial with an extractable volume of more than 1 mL. Then 0.5 mL will be withdrawn from this vial.

- Placebo: 0.9% NaCl solution (Groups 6, 8, and 10): 0.5 mL

Study vaccine will be administered by IM injection into the deltoid muscle, preferably of the non-dominant arm. Subsequent vaccinations are preferably administered in the opposite arm. If an injection cannot be given in the deltoid muscle due to a medical or other contraindication (for

example, tattooed upper arms rendering it difficult to assess site reactogenicity), use alternative locations such as the hip, thigh or buttocks. If alternative locations are used for vaccine administration, these locations should consistently be used for later vaccinations.

For information on vaccination windows, see Section 8, Study Assessments and Procedures.

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[0] 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 vaccine 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. 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 adults, the randomization will be balanced by using randomly permuted blocks and will be stratified by study site and age group (approximately two thirds of participants ≥18-≤55 years of age and one third of participants ≥65 years of age per group). For the adolescent cohort, the randomization will be balanced by using randomly permuted blocks and will be stratified age group (half of participants 12 to 15 years of age inclusive and half of participants 16 to 17 years of age inclusive per group).

From the time of protocol Amendment 2, for each of the age strata (16 to 17 years and 12 to 15 years) in the adolescent cohort, the safety of the Ad26.COV2.S vaccine at a dose level of $2.5x10^{10}$ vp (Group A-C) or $5x10^{10}$ vp (Group D-F) was planned to be evaluated by dose escalation in a sequential manner initially in groups of sentinels (11 participants in each group) and subsequently if the safety profile is favorable, in a group of 22 participants that will form the safety cohort (randomization ratio of 5:5:1 for both sentinels and safety cohorts). Safety was to initially be assessed in older adolescents (16 to 17 years of age) before proceeding with evaluation of safety in cohorts of younger adolescents (12 to 15 years of age). If, the safety profile is found to be acceptable, enrollment of study participants in Groups D-F was to start.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16-17 year old age group at a dose of $2.5x10^{10}$ vp enrolled in this study, the entire COVID-19 vaccine program was paused to evaluate a safety concern of TTS in adults. During this pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated (see current version of Investigator's Brochure[0]). While the IDMC endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level, the sponsor has decided not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose in Study VAC31518COV2001 and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12-17 years of age, and no

further enrollment of this age group will take place in this study. Therefore, per protocol Amendment 6, the 33 adolescents already enrolled at the time of Amendment 6 will continue to be followed in this study in accordance with the planned Schedule of Activities (Sections 1.3.5 and 1.3.6), but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at $2.5x10^{10}$ vp.

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 adult participant and at the planned time of randomization of the first adolescent participant, randomization may be started based on a paper randomization list until the IWRS is live. 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.

Blinding

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

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

Under normal circumstances, the blind should not be broken until the database is finalized or until unblinding to primary vaccination regimen (with the implementation of Amendment 5).

With implementation of protocol Amendment 5, adult participants who were initially enrolled to receive placebo (Groups 6, 8 and 10), will be offered a 2-dose (28-day interval) Ad26.COV2.S vaccination regimen at the $5x10^{10}$ vp dose level.

With the implementation of Amendment 5, all adult participants will be unblinded to the primary vaccination regimen. Adults who received active vaccine in the primary vaccination regimen will receive an antigen presentation injection with $1.25x10^{10}$ vp Ad26.COV2.S (Groups 1-5, 7, 9) in an unblinded manner, and adults who received placebo in the primary vaccine regimen, will receive a 2 dose active Ad26.COV2.S vaccine regimen at a 28-day interval and at a dose level of $5x10^{10}$ vp,

in an open-label manner. Per group, approximately one third of participants will be 65 years and older.

Similarly, all adolescents will initially be randomized and enrolled in a blinded manner to receive either an active vaccine or placebo in a 1-dose or 2-dose primary vaccination regimen (56-day interval). With implementation of Amendment 6 (at approximately 6 months of study participation), the 33 enrolled adolescent participants will be unblinded to the primary vaccination regimen. At this time, adolescent participants who were initially enrolled to receive placebo (Group C), will receive a single dose of Ad26.COV2.S vaccination regimen at the 2.5 $x10^{10}$ vp dose level.

The investigator may in an emergency determine the identity of the intervention by contacting the IWRS or by opening the sealed code (if IWRS is not available yet). The date, time, and reason for the unblinding must be documented in the appropriate section of the eCRF, and in the source document. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IWRS, and in the source document.

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

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

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

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

be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see Section 6.9).

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving 2 different COVID-19 vaccines. Participants who were already unblinded for any reason may receive Ad26.COV2.S vaccine upon discussion with the investigator, provided that they did not receive another COVID-19 vaccine. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the Schedule of Activities to the extent that the participant is amenable. All data will be analyzed separately from the point of unblinding for safety and immunogenicity, as described in the SAP.

6.4. Unblinding and Open-label Phase

With the implementation of protocol Amendment 5, all adult participants will be unblinded at the on-site unblinding visit. Participants who received active vaccine will then resume the schedule in Section 1.3.1, 1.3.2, or 1.3.3, as appropriate. Participants who received placebo will start following the Schedule of Activities for the active vaccine regimen in Section 1.3.4. Participants who were already unblinded for any reason may receive Ad26.COV2.S vaccine upon discussion with the investigator, provided that they did not receive another COVID-19 vaccine.

With implementation of Amendment 6 (at approximately 6 months of study participation), the 33 enrolled adolescent participants will be unblinded to the primary vaccination regimen. At this time, adolescent participants who were initially enrolled to receive placebo (Group C) will receive a single dose of Ad26.COV2.S vaccination regimen at the 2.5 $x10^{10}$ vp dose level and will continue the schedule in Section 1.3.6.

Before the actual participant unblinding, all of the previously available data should be complete and accurate in the participant's eCRF.

6.5. Study Vaccination 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 the location used for injection [deltoid or alternative location]). For blinding procedures, see Section 6.3, Measures to Minimize Bias: Randomization and Blinding.

6.6. Dose Modification

Dose modification is not applicable for adults.

Following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16-17 year old age group at a dose of 2.5x10^{10} vp enrolled in this study, the entire COVID-19 vaccine program was paused to evaluate a safety concern of TTS in adults. During this pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated (see current version of Investigator's Brochure[0]). While the IDMC endorsed further enrollment of adolescents

that would receive Ad26.COV2.S at a $5x10^{10}$ vp dose level (see Section 4.1), the sponsor has decided not to evaluate the $5x10^{10}$ vp dose level in pediatric participants based on the immunogenicity data from the $2.5x10^{10}$ vp dose in Study VAC31518COV2001 and has decided to redesign the pediatric studies. Study VAC31518COV3006 will focus on adolescent participants 12-17 years of age, and no further enrollment of this age group will take place in this study. Therefore, per protocol Amendment 6, the 33 adolescents already enrolled at the time of Amendment 6 will continue to be followed in this study in accordance with the planned Schedule of Activities (Sections 1.3.5 and 1.3.6), but no further vaccination with Ad26.COV2.S will occur in Groups A and B. Participants in Group C will receive a single dose of Ad26.COV2.S at $2.5x10^{10}$ vp.

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

Adults in the placebo groups (Groups 6, 8 and 10) will receive a 2-dose active Ad26.COV2.S vaccine regimen at a 28-day interval and at a dose level of $5x10^{10}$ vp, in an open-label manner All adult participants will be followed up for safety until 6 months after the second dose of active vaccine (see Schedule of Activities, Section 1.3.4). Adolescent participants who were initially enrolled to receive placebo (Group C), will receive a single dose of Ad26.COV2.S vaccination regimen at the 2.5 $x10^{10}$ vp and $5x10^{10}$ vp dose level, respectively, at approximately 6 months of study participation. All adolescent participants will be followed up for safety until approximately 12 months post vaccination 1 (see Schedule of Activities, Section 1.3.7).

As COVID-19 vaccines become authorized/licensed for use, some participants may become eligible to receive such vaccines, 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 should request individual unblinding to take up the offer of an authorized/licensed COVID-19 vaccine. Participants who were already unblinded for any reason may receive Ad26.COV2.S vaccine upon discussion with the investigator, provided that they did not receive another COVID-19 vaccine. All data will be analyzed separately from the point of unblinding for safety, efficacy and immunogenicity (under the conditions outlined in Section 6.3), as described in the SAP.

6.8. 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 1 hour and will be closely monitored for allergic or other reaction by study staff. Follow-up telephone calls 12 hours and 24 hours post vaccination will be made).
- Document the quantity of the excess dose in the eCRF.
- Report as a special reporting situation.

6.9. 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 the first dose of study vaccine must be recorded at screening.

Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of vaccination and for 28 days after the subsequent dose of study vaccine. All other concomitant therapies should also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs or suspected AESIs reported per protocol requirements outlined in Section 8.3.1.

Use of any experimental medication (including experimental vaccines other than the study vaccine) will lead to discontinuation of administration of any subsequent study vaccination. Any participant who has been given an anti-COVID-19 vaccine (other than study vaccine) or treatment will not receive further study vaccination. Participants may not receive an investigational drug (including investigational drugs for prophylaxis of COVID-19) or use an invasive investigational medical device within 30 days or receive an investigational 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.

Licensed live attenuated vaccines should be given at least 28 days before or at least 28 days after a study vaccination. Other licensed (not live) vaccines (eg, 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. The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination and during the study. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

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[18] 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

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

vaccine. If any of these agents are indicated in a disease setting, these must take priority over the study vaccine.

Refer to Section 5.2, Exclusion Criteria for further details of prohibited therapy.

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

6.10. Study Vaccination Pausing Rules

The PI and the study responsible physician/scientist (SRP/S) 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 SMC, after which the SMC will recommend whether the pause can be lifted or not, or whether other steps are needed.

The SMC will review blinded data first, but has the right to request the randomization codes and review unblinded data if deemed necessary. The SMC 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 SMC meeting triggered by the occurrence of a given pausing rule, the SMC 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 of adolescent participants only. Laboratory abnormalities noted below refer to cases where the study-site personnel perform laboratory safety testing for investigation of an AE.

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 SMC information. Upon their review, the SMC 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 (ie, the day of occurrence of the AE is counted as Day 1) [19]; OR
7. A study pause is triggered in the ongoing clinical studies.

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 SMC review of similar AE, 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 the 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 SMC members and coordination of a SMC 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 SMC 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 SMC, participant safety may be threatened.

Resumption of vaccinations will start only upon receipt of written recommendations by the SMC. If any pausing rule is met and, if following appropriate safety review it is deemed appropriate to

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

restart dosing, the sponsor must submit a request to restart dosing with pertinent data to competent authority as a request for a substantial Amendment, as required by local regulations or authority request (eg, the Medicines and Healthcare products Regulatory Agency [MHRA]). If needed, this will be followed by a substantial amendment of the IB and/or protocol. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. These communications from the SMC will be forwarded by the investigator to the IRB/IEC and by the sponsor to the relevant health authorities, according to local standards and regulations. For further details, refer to Section 10.3.6 in Appendix 3.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

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

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Participant was unblinded and received an authorized/licensed COVID-19 vaccine
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic or recurrent use of systemic corticosteroids at immunosuppressive dose, and administration of antineoplastic and immunomodulating agents or radiotherapy
- Withdrawal from further study vaccination
- During the double-blind period, participant has a positive test result for SARS-CoV-2 infection during the study (see Section 8.1.2, Procedures in Case of COVID-19-like Signs and Symptoms)
- Participant receives any experimental medication (including experimental vaccines other than the study vaccine) or receives an anti-COVID-19 vaccine or treatment
- Participant previously experienced TTS or heparin-induced thrombocytopenia (HIT)
- Participant has a history of capillary leak syndrome (CLS), or experienced CLS after a study vaccination.

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/assent from the study
- Death
- Repeated failure to comply with protocol requirements

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent/assent, then no additional assessments are allowed, but an optional safety visit will still be offered.

Withdrawal of Consent/assent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent/assent. Alternate follow-up mechanisms that the participant agreed to when signing the consent/assent 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/assent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

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

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of safety, reactogenicity, immunogenicity and other measurements applicable to this study. All participants in the study will be counseled on COVID-19 prevention each time that they have a contact with study site staff in line with local guidelines.

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/legal guardian(s) (where appropriate for adolescent participants) to avoid missing or incorrect data. The diary will be reviewed by the study personnel at visits indicated in 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 for documentation of body temperature and pulse oximetry results) and a kit to collect nasal swabs if they experience COVID-19-like symptoms during the study (see Section 8.1.2and Section 8.1.2.1). Baseline pulse oximetry will be conducted at Visit 1.

For adults, the total blood volume to be collected over the course of the study will be approximately:

- Groups 1-5

  460.5 mL for the subset of participants for which both humoral and cellular immunogenicity (PBMC) will be assessed,

  155.5 mL for the subset of participants in which only humoral immunogenicity will be assessed;

- Group 6

  563 mL for the subset of participants for which both humoral and cellular immunogenicity (PBMC) will be assessed,

  258 mL for the subset of participants in which only humoral immunogenicity will be assessed;

- Groups 7 and 9:140.5 mL;
- Groups 8 and 10: 243 mL.

For adolescents in Groups A and B, the total blood volume will be approximately 68 mL. The total blood volume will be approximately 87 mL for participants in Group C.

For adult participants in Groups 1-10 and adolescent participants in Groups A-C who need a repeat serological test at Day 1, an additional 8 mL of blood will be drawn. For participants with (suspected) COVID-19, additional blood samples of a total of 35 mL (adults) or 20 mL (adolescents) might be collected. For participants who experience a suspected AESI, up to an additional 30 mL of blood may be collected. Refer to Section 1.3, Schedule of Activities for the total blood volume (serum and, as applicable, PBMC and whole blood samples) to be collected at each visit and over the complete course of the study for each group and in case of COVID-19-like symptoms. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

Visit Windows

Visit windows that will be allowed are summarized below. The participant should be encouraged to come on the exact day planned and use the visit window only if absolutely necessary.

The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination. If a participant misses a vaccination, the post-vaccination visits will be 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 6.10), efforts will be made to still vaccinate the participant as soon as possible, even if out of window. 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.

In October 2020, the current study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2 (Visit 4), rendering the intent of the 28-day vaccination interval in these groups futile. As their actual vaccination might coincide with the intervals from

other groups, it might be possible to use the data according to that interval. In this case, further details will be provided in the SAP.

Table 4: Visit Windows Groups 1 to 6 (56-day interval schedule [2- and single-dose regimens]) – Adults

Visit	Visit Day	Allowed Window	Primary Purpose
3[a]	8	±2 days	7 days post-vaccination 1 safety visit
4	15	±3 days	14 days post-vaccination 1 safety and immunogenicity visit
5	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
6	57	-3/+7 days	Vaccination 2
7[a]	64[b]	±2 days	7 days post-vaccination 2 safety and immunogenicity visit
8	71[b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
9	85[b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
10	169[b]	±14 days	Antigen Presentation (Groups 1-5) or Placebo (Group 6)
11[a]	176[b]	±2 days	7 days post antigen presentation safety and immunogenicity visit
12	197[b]	±3 days	28 days post antigen presentation safety and immunogenicity visit
UB			Unblinding to primary vaccination regimen*
13	337[b]	±21 days	6 months post antigen presentation safety phone call
101	UB1		Unblinded vaccination 1
102	UB8[c]	±2 days	7 days post unblinded vaccination 1 safety and immunogenicity visit
103	UB29	-3/+7 days	Unblinded vaccination 2
104	UB36[c]	±2 days	7 days post unblinded vaccination 2 safety visit
105	UB43[c]	±3 days	14 days post unblinded vaccination 2 safety and immunogenicity visit
106	UB57[c]	±3 days	28 days post unblinded vaccination 2 safety and immunogenicity visit
107	UB169[c]	±21 days	6 months post unblinded vaccination 1 safety and immunogenicity visit
14	393[b]	±21 days	12 months post-vaccination 2 safety and immunogenicity visit

Placebo Group 6 only

* With the implementation of Amendment 5

a. If a participant comes in early for Visit 3, 7, or 11, ie, 1 or 2 days prior to the 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 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 and antigen presentation will be determined relative to the actual day of that vaccination/antigen presentation.

c. The timings of visits after the third and fourth vaccination will be determined relative to the actual day of that vaccination (UB1).

Table 5: Visit Windows Groups 7 and 8 (28-day interval schedule) – Adults

Visit	Visit Day	Allowed Window	Primary Purpose
3[a]	8	±2 days	7 days post-vaccination 1 safety visit
4	29	±3 days	Vaccination 2
5[a]	36[b]	±2 days	7 days post-vaccination 2 safety and immunogenicity visit
6	43[b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
7	57[b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
8	141[b]	±14 days	Antigen presentation (Group 7) or Placebo (Group 8)
9[a]	148[b]	±2 days	7 days post antigen presentation safety and immunogenicity visit
10	169[b]	±3 days	28 days post antigen presentation safety and immunogenicity visit
UB			Unblinding to primary vaccination regimen
101	UB1		Unblinded vaccination 1
102	UB8[c]	±2 days	7 days post unblinded vaccination 1 safety and immunogenicity visit
103	UB29	-3/+7 days	Unblinded vaccination 2
104	UB36	±2 days	7 days post unblinded vaccination 2 safety visit
105	UB43	±3days	14 days post unblinded vaccination 2 safety and immunogenicity visit
106	UB57[c]	±3 days	28 days post unblinded vaccination 2 safety and immunogenicity visit
11	309[b]	±21 days	6 months post antigen presentation safety phone call
107	UB169[c]	±21 days	6 months post unblinded vaccination 1 safety and immunogenicity visit
12	365[b]	±21 days	12 months post-vaccination 2 safety and immunogenicity visit
Placebo Group 8 only			

* With the implementation of Amendment 5

a. If a participant comes in early for Visit 3, 5, or 9, ie, 1 or 2 days prior to the 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 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 and antigen presentation will be determined relative to the actual day of that vaccination/antigen presentation.

c. The timings of visits after the third and fourth vaccination will be determined relative to the actual day of that vaccination (UB1).

Table 6: Visit Windows Groups 9 and 10 (84-day interval schedule) – Adults

Visit	Visit Day	Allowed Window	Primary Purpose
3[a]	8	±2 days	7 days post-vaccination 1 safety visit
4	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
5	85	-3/+7 days	Vaccination 2
6[a]	92[b]	±2 days	7 days post-vaccination 2 safety and immunogenicity visit
7	99[b]	±3 days	14 days post-vaccination 2 safety and immunogenicity visit
8	113[b]	±3 days	28 days post-vaccination 2 safety and immunogenicity visit
9	197[b]	±14 days	Antigen presentation (Group 9) or Placebo (Group 10)
10[a]	204[b]	±2 days	7 days post antigen presentation safety and immunogenicity visit
11	225[b]	±3 days	28 days post antigen presentation safety and immunogenicity visit
UB			Unblinding to primary vaccination regimen
101	UB1		Unblinded vaccination 1
102	UB8[c]	±2 days	7 days post unblinded vaccination 1 safety visit
103	UB29	-3/+7 days	Unblinded vaccination 2
104	UB36[c]	±2 days	7 days post unblinded vaccination 2 safety visit
105	UB43[c]	±3 days	14 days post unblinded vaccination 2 safety and immunogenicity visit
106	UB57[c]	±3 days	28 days post unblinded vaccination 2 safety and immunogenicity visit
107	UB169[c]	±21 days	6 months post unblinded vaccination 1 safety and immunogenicity visit
12	365[b]	±21 days	6 months post antigen presentation safety phone call
13	421[b]	±21 days	12 months post-vaccination 2 safety and immunogenicity visit

Placebo Group 10 only

* With the implementation of Amendment 5

a. If a participant comes in early for Visit 3, 6, or 10, ie, 1 or 2 days prior to the 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 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 and antigen presentation will be determined relative to the actual day of that vaccination/antigen presentation.

c. The timings of visits after the third and fourth vaccination will be determined relative to the actual day of that vaccination (UB1).

Table 7: Visit Windows Groups A-C – Adolescents[20]

Visit	Visit Day	Allowed Window	Primary Purpose
3	4	0 days	3 days post-vaccination safety phone call assessment of sentinels
4[a]	8	±2 days	7 days post-vaccination 1 safety visit
5	29	±3 days	28 days post-vaccination 1 safety and immunogenicity visit
6	57	-3/+7 days	56 days post-vaccination 1 safety and immunogenicity visit
7	85	±3 days	84 days post-vaccination 1 safety and immunogenicity visit
At approximately 6 months* of Study Participation Unblinding to primary vaccination regimen			
8	169	±3 days	6 months post-vaccination 1 safety and immunogenicity visit
101	169[b]	-3/+7 days	Unblinded vaccination
102	176[b]	2 days	7 days post unblinded vaccination 1 safety visit
103	197[b]	±3 days	28 days post unblinded vaccination safety and immunogenicity visit
104	225[b]	-3/+7 days	56 days post unblinded vaccination safety and immunogenicity visit
105	253[b]	±3 days	84 days post unblinded vaccination safety and immunogenicity visit
9	253	±21 days	9 months post-vaccination 1 safety phone call
106	337[b]	±3 days	6 months post unblinded vaccination safety and immunogenicity visit
10	337	±14 days	12 months post-vaccination 1 safety and immunogenicity visit
Placebo Group C only			

*With implementation of Amendment 6 (at approximately 6 months of study participation)

a. If a participant comes in early for Visit 4 (ie, 1 or 2 days prior to the 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 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 active vaccination of placebo Group C will be determined relative to the actual day of that vaccination.

Screening

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

Screening may be conducted in part via a sponsor- and IRB/IEC-pre-approved non-study-specific screening consent process, but only if the relevant pre-screening tests are identical to the per protocol screening tests and are within 4 weeks prior to first vaccination. However, no study-specific procedures, other than these pre-approved pre-screening assessments, will be performed until the participant has signed the study-specific ICF. The molecular test for the presence of SARS-CoV-2 infection must be done within 4 days before vaccination[21]. Participants

[20] Not applicable in Germany and the Netherlands

[21] 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 requires serologic testing outside of the protocol-mandated testing schedule, the site will guide them on the appropriate assay that identifies the viral nucleocapsid protein (and not the spike protein).

who test positive 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, the 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)
- An approved pulse oximeter, if necessary
- Pharmacy manual/SIPPM
- Laboratory manual
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- Participant diaries
- Nasal swab kit
- Participant instructions and booklet: COVID-19-like signs and symptoms daily surveillance, nasal swab instructions, SIC (for daily completion, if symptomatic), and for documentation of temperature and pulse oximetry
- Contact information pages

8.1. Immunogenicity Assessments

8.1.1. Immunogenicity Assessments

Venous blood samples will be collected for assessment of humoral immune responses and cellular immunogenicity (RNA sequencing) in all participants. Blood for evaluation of humoral and cellular (PBMC in subset only) immune responses will be drawn from participants at the time points specified in the Schedule of Activities. Cellular immune responses (PBMC) will only be

assessed in a subset of adult participants in Groups 1-6 (approximately 112; 21 participants per group in Groups 1-5, 7 participants in Group 6; at selected sites) Immunogenicity assessments may include, but are not limited to, the humoral and cellular immunogenicity assays (as available and feasible) summarized in the below table. Sample volumes and time points are detailed in the Schedules of Activities in Section 1.3.

If the participant is unable to complete the study without withdrawing consent/assent, 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 8.

Table 8: Summary of Humoral and Cellular Immunogenicity Assays

Assay	Purpose
Humoral Immunogenicity	
Primary/Secondary/Exploratory endpoints	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein)
Exploratory endpoints	
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 N protein, if such an assay is available
SARS-CoV-2 binding antibodies (MSD)	Analysis of antibodies binding to the SARS-CoV-2 S protein (different than the assays supportive of the secondary objectives) and the RBD of the SARS-CoV-2 S protein
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
SARS-CoV-2 neutralizing antibodies	Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants
Adenovirus neutralization (neutralization assays)	Analysis of neutralizing antibodies to adenovirus
Cellular Immunogenicity	
Exploratory endpoint	
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
Gene expression analysis	Analysis of gene expression by RNA transcript profiling

CD = cluster of differentiation; ELISA = enzyme-linked immunosorbent assay; IFNγ = interferon gamma; IL = interleukin; MSD = meso scale discovery; PBMC = peripheral blood mononuclear cell; RBD = receptor-binding domain; RNA = ribonucleic acid; S = Spike protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; Th = T helper; TNFα = tumor necrosis factor alpha; VNA = virus neutralization assay

8.1.2. Procedures in Case of (Suspected) COVID-19

Participants will be provided with a booklet including a daily question on whether they are experiencing COVID-19-like symptoms, and for documentation of body temperature and pulse oximetry results. Baseline pulse oximetry will be conducted at Visit 1. During the study, study-site personnel will remind participants to complete the SIC in the event of any signs and symptoms and to contact the site at the time of symptom onset or in case of a positive RT-PCR test for SARS-CoV-2 (regardless of where the testing was performed). This positive RT-PCR test will need to be captured in the eCRF.

If a participant meets one of the prespecified criteria for (suspected) COVID-19[22] (see Section 8.1.2.1), the following should take place (for details, see the Schedule of Activities in Section 1.3.7):

- Participants should contact the study site at the time of symptom onset/at time of becoming aware of the positive RT-PCR test.
- If the trigger was a sign or symptom: a nasal swab should be collected by 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. It is preferred that the swab is taken by a caregiver (spouse, partner, relative, friend, or health care professional). If that is not possible, the participant can collect the swab himself or herself. The nasal swab sample collection and storage instructions will be described separately. The site should arrange transfer of the sample to the study site as soon as possible after sample collection. If the trigger was a positive RT-PCR test, then this first nasal swab is not needed.
- A second nasal swab will be obtained on COVID-19 Day 3-8 following the same procedures as the first nasal swab. The second nasal swab may also be collected at home, at the hospital, or at another location, if needed, by a study site staff, if appropriate procedures are in place. The presence of SARS-CoV-2 infection will be assessed at the study site by molecular testing using the nasal swab samples. The nasal swabs may be tested at the central laboratory for the presence of SARS-CoV-2 and other respiratory pathogens using a broad respiratory pathogens panel. 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. A physical examination, vital signs measurements and pulse oximetry will be performed and a blood sample for assessment of the humoral immune response and other biomarkers will be taken.
- From COVID-19 Day 3-8 onwards: Additional swabs should be taken by a healthcare professional from the participant as soon as possible, but with a minimum of 1 day between the swabs, until 2 consecutive negative swabs are obtained, ie, twice weekly or more frequently until resolution. These precautionary measures are to ensure that site staff who

[22] 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.

come into physical contact with a participant deemed to be a COVID-19 case undertake the proper safety procedures such as wearing of personal protective equipment.

- Participants should complete the SIC (see Section 10.7) and record their highest body temperature daily starting on the first day of trigger onset. Blood oxygen saturation and pulse rate should be measured using a pulse oximeter 3 times a day, preferably in the morning, at lunch time, and in the evening.
- Collection of data will continue until resolution of the COVID-19 episode, defined as having 2 consecutive days with no COVID-19-related signs or symptoms and 2 consecutive SARS-CoV-2 negative nasal swabs.
- For participants with a positive test result for SARS-CoV-2 infection, a study visit will be conducted 28 days after trigger onset to assess the clinical course of the infection, record concomitant medications since trigger onset, and obtain a blood sample for assessment of the humoral immune response (VNA, ELISA, and Fc functionality) and other biomarkers (RNA-seq). 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 will be notified and may be requested to remain at home and not visit the study site. If necessary, study-site personnel will visit the participant at home[23]. Under these circumstances, the participant will be contacted by the site at least once per week and the participant's medical care provider will be notified. The participant will not receive further study vaccinations but should remain on study for follow-up with assessments of safety and immunogenicity. The participant will be followed until resolution of clinical symptoms. The sponsor recommends to follow these participants until 2 consecutive SARS-CoV-2 negative nasal swabs could be obtained.

If a participant has a positive test result for a respiratory infection other than COVID-19, study visits will continue per the Schedule of Activities (Section 1.3).

8.1.2.1. Prespecified Criteria for (Suspected) COVID-19

The criteria for (suspected) COVID-19 (ie, the triggers to start procedures explained in Section 8.1.2) are prespecified as follows:

[23] The study staff visiting participants at home will use personal protective equipment according to local regulations.

Positive RT-PCR result for SARS-CoV-2, regardless where the testing was performed (under the auspices of the study or through a private or public laboratory independent of the study), whether symptomatic or asymptomatic

OR

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

- Headache
- Malaise (appetite loss, generally unwell, fatigue, physical weakness)
- Myalgia (muscle pain)
- Chest congestion
- Cough
- Runny nose
- Shortness of breath or difficulty breathing (resting or on exertion)
- Sore throat
- Wheezing
- Eye irritation or discharge
- Chills
- Fever (≥38.0°C or ≥100.4°F)
- Pulse oximetry value ≤95%, which is a decrease from baseline
- Heart rate ≥90 beats/minute at rest, which is an increase from baseline
- Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)
- Neurologic symptoms (numbness, difficulty forming or understanding speech)
- Red or bruised looking toes
- Skin rash
- New or changing olfactory or taste disorders
- Symptoms of blood clots: pain/cramping, swelling or redness in your legs/calves
- Confusion
- Bluish lips or face
- Clinical suspicion/judgment by investigator of symptoms suggestive of COVID-19, including MIS-C (multisystem inflammatory syndrome in children [adolescent participants only])

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

8.1.3. Asymptomatic SARS-CoV-2 Infection

A non-S protein ELISA (eg, SARS-CoV-2 N-ELISA), will be performed to identify cases of asymptomatic SARS-CoV-2 infection (see also Table 8). For adults, this assay will be performed on samples obtained on Day 1, 28 days after antigen presentation, and 6 months after Vaccination 2. For adolescents, this assay will be performed on samples obtained on Day 1, 28 days after Vaccination 2, at Vaccination 3, and 6 months after Vaccination 3.

Any asymptomatic participant with a positive RT-PCR result for SARS-CoV-2, regardless of where the testing was performed (under the auspices of the study or through a private or public laboratory independent of the study) will be considered. The positive RT-PCR result will need to be captured in the eCRF.

8.2. Safety Assessments

Details regarding the SMC are provided in Section 10.3.6.

AEs will be reported and followed by the investigator as specified in Section 8.3 and Section 10.4.

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

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

The study will include the following evaluations of safety and reactogenicity according to the time points provided in the Schedule of Activities (Section 1.3).

8.2.1. Physical Examinations

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

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

Physical examinations will be performed by the investigator or designated medically trained clinician. Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF.

8.2.2. Vital Signs

Body temperature (oral route preferred, or in accordance with the local standard of care), pulse/heart rate, respiratory rate, and blood pressure will be assessed.

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

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.

For an adolescent participant who becomes pregnant, this information will be shared with the study participant's legal guardian as required or permitted by local regulations.

8.2.4. Hematology Clinical Laboratory Assessments

Blood samples for hematology (as detailed in Section 10.2) to evaluate D-dimers and Lupus anticoagulant, anti-β2 glycoprotein, anti-cardiolipin (adults) and anti-PF4 (adults and adolescents) will be collected at the timepoints indicated in the Schedules of Activities (see Section 1.3). For timepoints that have already passed before protocol Amendment 2 was approved and implemented, the D-dimers, Lupus anticoagulant, and anti-PF4 tests will not be performed retrospectively, as these tests are to be performed in plasma samples. Serum samples originally drawn or yet to be drawn for the humoral immunogenicity assessments will be used for the testing of Anti-β_2 glycoprotein, anti-PF4 and anti-cardiolipin. Collection of plasma and serum samples for testing of D-dimers, Lupus anticoagulant, Anti-β_2 glycoprotein, anti-PF4, and Anti-cardiolipin will be performed for all groups from the time of approval of Amendment 3.

The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE or medical history section of the case report form (CRF), as applicable.

In case of a thrombotic event or TTS, 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 10.13, Appendix 13) 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 1.3.8 and Section 10.2, Appendix 2). The Investigator will review the laboratory test results to assist the investigation of the AESI.

See Section 8.3.6.1 for details on laboratory test details to be reported for an AE of thrombocytopenia.

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, suspected AESIs, SAEs, and product quality complaint (PQC), 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.

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

All Adverse Events

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported for all participants from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.

Clinically relevant medical events not meeting the above criteria and occurring between signing of the ICF and moment of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

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

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

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported for all participants from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

Adverse Events of Special Interest

From the time of local approval of protocol Amendment 5 onwards, TTS is considered to be an AESI. Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/μL[0]]) will be recorded from the moment of vaccination 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 CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

Adolescents

Signs and symptoms of Multisystem Inflammatory Syndrome in Children (MIS-C) will be monitored and reported as SAE in children with (suspected) COVID-19 as confirmed by a positive RT-PCR result for SARS-CoV-2, and in children of mothers or close relatives with prior (within 4-weeks) or current suspected or confirmed COVID-19. Further details on case definition and reporting of MIS-C in children can be found in section 10.12.

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 1 hour for the presence of any acute reactions and solicited events.

In addition, participants (or parents/legal guardians of the minor 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 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.[0,0]

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.[0]

After each vaccination, participants will remain under observation at the study site for at least 1 hour to monitor for the presence of any acute reactions and solicited events.

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 in the participant diary.

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, suspected AESI, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs, including pregnancy, will be followed by the investigator as specified in Section 10.4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study vaccination.

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 class effects, or based on nonclinical signals. AESIs 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 (TTS)

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.

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 10.13, Appendix 13. A suspected TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 10.14, Appendix 14 OR,
- Thrombocytopenia, defined as platelet count below 150,000/μL[0]

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 10.13, Appendix 13 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, or TTS reported prior to protocol Amendment 5.

8.4. Virology Assessments

Nasal swabs collected by or from participants with COVID-19-like symptoms may be tested at the central laboratory for the presence of SARS-CoV-2 and other respiratory pathogens using a broad respiratory pathogens panel.

8.5. Biomarkers

For participants with a positive test result for SARS-CoV-2 infection, blood will be drawn for evaluation of biomarkers (eg, those associated with severe COVID-19), as indicated in Section 1.3.7).

8.6. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No formal hypothesis testing will be performed in this study.

9.2. Sample Size Determination

The number of adult participants chosen for this study will provide a preliminary safety and immunogenicity assessment.

Sample size for the adolescent participants was originally calculated based on assessment of non-inferiority of immune responses with adults; however, following the initial vaccination of the first 33 adolescent participants (sentinels + safety cohort) in the 16-17 year old age group at a dose of $2.5x10^{10}$ vp, the entire COVID-10 vaccine program, was paused to evaluate the safety concern of TTS in adults. During the pause, the safety and immunogenicity data for these 33 adolescent participants was evaluated (see current version of Investigator's Brochure[0]). Based on these results, the sponsor decided to cease enrollment of additional adolescents in this study. Instead, further evaluation of safety, reactogenicity and immunogenicity in pediatric populations, including dose selection of Ad26.COV2.S, will proceed under separate study protocols.

9.2.1. Immunogenicity

The primary objective in the adult population of the study is to explore the dose-response and interval-response relationship of humoral immune responses induced by different dose levels and different vaccine administration timings of Ad26.COV2.S using VNA titers and ELISA U/mL.

To explore the dose-response relationship between VNA/ELISA and different dose levels of the Ad26.COV2.S vaccine, a separate linear regression model will be fitted for:

- all active groups 14 days post vaccination 1
- all active groups 28 days post vaccination 1
- the 2-dose active groups using data of Groups 1-3, 28 days post vaccination 2
- the single-dose active groups using data of Groups 4-5, 28 days post vaccination 2
- the 2-dose active groups, using data of groups 1-3, 14 days post vaccination 2

In the linear regression model the log transformed VNA/ELISA titers at each timepoint will be used as dependent variable and the dose levels as independent variable.

Depending on the model fit, other models (eg, log-linear models or EMAX models) may be explored as well for the 56-day interval regimen.

Details on the comparison between the different dose levels and vaccination interval groups will be outlined in the SAP.

9.2.2. Safety

Placebo recipients are included for blinding and safety purposes and will provide additional control specimens for the 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. The observation of 0 events (eg, SAEs) is associated with 95% confidence that the true event rate is below the rates specified in Table 9 for the considered number of participants.

Table 9 : Upper Limit of the 95% One-sided Confidence Interval if no Cases are Observed for Different Sample Sizes

Sample Size	N=25	N=50	N=75	N=150
Upper Limit 95% one-sided CI	11.3%	5.8%	3.9%	2.0%

CI = confidence interval, N = number of participants

Table 10 provides the probability of observing at least one AE in a group of the considered sample size given several true AE rates.

Table 10: Probability of Observing at Least One AE in a Group of the Considered Sample Size Given Several True AE Rates

True AE Rate (%)	Probability of Observing at Least One AE in N Participants (%)			
	N=25	N=50	N=75	N=150
0.5	12	22	31	53
1	22	39	53	78
2.5	47	72	85	98
10	93	99	>99.9	>99.9
25	>99.9	>99.9	>99.9	>99.9
50	>99.9	>99.9	>99.9	>99.9

AE = adverse event, N = number of participants

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[24]: The per protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with natural SARS-CoV-2 infection occurring after screening (if applicable) will be excluded from the analysis.

9.4. Statistical Analyses

The SAP will be finalized prior to the first data base lock (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. Safety and immunogenicity sub-analyses will also be performed by age category. Immunogenicity sub-analyses will also be performed by BMI, ethnicity, and other factors as will be described in the SAP.

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

With the implementation of Amendment 5, all adult participants will be unblinded to the primary vaccination regimen, and adults who received placebo in the primary vaccine regimen will receive a 2-dose active Ad26.COV2.S vaccine regimen at a 28-day interval and at a dose level of $5x10^{10}$ vp, in an open-label manner, at which point the sponsor will also be unblinded.

With the implementation of Amendment 6, the 33 adolescent participants will be unblinded to the primary vaccination regimen, and those who received placebo (Group C) will receive a single dose of active Ad26.COV2.S at a dose level of $2.5x10^{10}$ vp, in an open-label manner. Limited pooled safety and reactogenicity data (planned for IDMC review) and group unblinded immunogenicity data (summary of S-ELISA, including GMC, and seroresponse rates for all participants and seronegative at baseline participants, in Ad26.COV2.S $2.5x10^{10}$ vp only) were reviewed by the sponsor prior to Amendment 6 (see Section 4.1 Overall Design).

9.4.2. Primary/Secondary Endpoints

Immunogenicity Endpoints

Descriptive statistics (geometric mean and confidence intervals, or median and interquartile range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters. Several definitions of serological response will be applied (fold increases in GMT [VNA] or GMC [ELISA]). 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 together with confidence intervals.

For adults, all data will be analyzed separately from the point of unblinding for safety and immunogenicity. Details will be described in the SAP.

For adolescents, limited pooled safety and reactogenicity data (planned for IDMC review) and group unblinded immunogenicity data (summary of S-ELISA, including GMC, and seroresponse rates for all participants and seronegative at baseline participants, in Ad26.COV2.S $2.5x10^{10}$ vp only) were reviewed by the sponsor prior to Amendment 6 (see Section 4.1 Overall Design).

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).

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 done on the FAS.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis. (S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately. For each AE, the percentage of participants who experience at least one 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, and AESI or an SAE (including Multisystem Inflammatory Syndrome in Children [MIS-C]; adolescents only).

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. Tertiary/Exploratory Endpoints

Detailed statistical methodology for analysis of exploratory endpoints will be described in the SAP.

9.4.4. 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 SAP.

Statistical analysis of biomarker responses (eg, RNA-seq responses) will be detailed in a separate SAP.

9.5. Planned Analysis

Interim and Primary Analyses for Adult Participants

An interim analysis of safety and immunogenicity will be performed, including all available immunogenicity data up to Day 29 (if applicable) and all available safety data post vaccination 1 of all groups in the adult cohort. Unblinded data at the vaccination group level will be available to the sponsor and might be used for regulatory submissions.

The primary analysis of safety and immunogenicity post-vaccination 2 will be performed when all adult participants have completed the visit that takes place 28 days after the second study vaccination in all groups or discontinued earlier. The analysis will include safety and immunogenicity data (VNA and ELISA) for all participants through Day 85 (Groups 1-6), Day 57 (Groups 7-8) or Day 113 (Groups 9-10). It will also include Th1-Th2 responses assessed only in Groups 1-6 (as available and feasible) through Day 85 (ie, 28 days after the second study vaccination). Unblinded data at the vaccination group level will be available to the sponsor and might be used for regulatory submissions.

A second interim analysis of safety and immunogenicity will be performed, including 28-day immunogenicity and 28-day safety data post antigen presentation of all groups.

The final analysis of the adult cohort will be performed when all included adult participants have completed the last visit or discontinued earlier.

Additional interim analyses may be performed for safety and/or immunogenicity to facilitate decision making with regards to the planning of future studies.

Analysis of the adolescent cohort will be performed when all included adolescent participants have completed the last visit or discontinued earlier.

Additional interim analyses may be performed for safety and/or immunogenicity to facilitate decision making with regards to the planning of future studies.

General

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 Support Group (SSG) will provide individual level unblinded data pertaining to study VAC31518COV2001 when unblinding at the participant level is required (see Section 10.3.6). 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 SMC as soon as an imbalance between groups is detected. Participants, clinical staff, and study-site personnel will remain blinded to the study vaccine allocation until implementation of protocol Amendment 5 (adults) or Amendment 6 (adolescents). A prespecified threshold (imbalance above a certain percentage and/or number of cases) that will trigger notification of the SMC will be described in the SAP.

The SAP will describe the planned analyses in greater detail.

Participants unblinded due to administration of an authorized/licensed COVID-19 vaccine

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

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving 2 different COVID-19 vaccines. Participants who were already unblinded for any reason may receive Ad26.COV2.S vaccine upon discussion with the investigator, provided that they did not receive a COVID-19 vaccine. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the Schedule of Activities to the extent that the participant is amenable. All data will be analyzed separately from the point of unblinding for safety and immunogenicity, as described in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	adenovirus type 26
ADCC	antibody-dependent cell-mediated cytotoxicity
AdVAC®	adenoviral vaccine (vector platform)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	antigen presentation
AST	aspartate aminotransferase
BMI	body mass index
BUN	Blood Urea Nitrogen
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CLS	Capillary leak syndrome
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CPK	creatine phosphokinase
eCRF	Electronic case report form(s)
CT	computed tomographic
DBL	data base lock
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
DRC	data review committee
DVT	deep vein thrombosis
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ERD	enhanced respiratory disease
EUA	Emergency Use Authorization
FAS	full analysis set
Fc	crystallizable fragment
FDA	Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GLP	good laboratory practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICS	intracellular cytokine staining
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IL	interleukin
IM	intramuscular
IND	Investigational New Drug

IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MERS (-CoV)	Middle East respiratory syndrome (coronavirus)
MIS-C	multisystem inflammatory syndrome in children
MSD	meso scale discovery
N	nucleocapsid
NI	non-inferiority
NIAID	National Institute of Allergy and Infectious Diseases
PBMC	peripheral blood mononuclear cells
PI	principal investigator
PPI	per protocol immunogenicity
PQC	product quality complaint
PRBC	packed red blood cells
PSRC	Prevention Science Review Committee
PT	prothrombin time
PTT	partial thromboplastin time
RBD	receptor-binding domain
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	real-time reverse-transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV(-2)	severe acute respiratory syndrome coronavirus(-2)
SIC	Symptoms of Infection with Coronavirus-19
SIPPM	site investigational product and procedures manual
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SRP/S	study responsible physician/scientist
SUSAR	suspected unexpected serious adverse reaction
Th	T helper
TNF-α	tumor necrosis factor alpha
TTS	thrombosis with thrombocytopenia syndrome
ULN	upper limit of the normal range
US	United States
VNA	virus neutralization assay
vp	virus particle
WBC	white blood cell
WHO	World Health Organization

10.2. Appendix 2: Hematology Clinical Laboratory Tests

Samples will be taken according to the SoA in Section 1.3. Samples will be analyzed by a central laboratory. The following tests may be performed:

Protocol-Required Hematology Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	All adult participants: o Lupus anticoagulans o Anti-β2 glycoprotein o Anti-cardiolipin o D-dimers o Anti-PF4 All adolescent participants: o Anti-PF4
	Adult and adolescent participants with a suspected AESI: • Serum/plasma samples for coagulation-related assays such as but not limited to*: o Activated partial thromboplastin time o Prothrombin time o International normalized ratio o Fibrinogen o Lupus anticoagulants o Anti-β2 glycoprotein o Anti-cardiolipin o D-dimers o Anti-PF4 o Heparin Induced Thrombocytopenia (HIT)/PF4 Ab, IgG·(HIT assay) o Platelet activation assay (if HIT/PF4 is positive) o Homocysteine o ADAMTS13 Activity and Inhibitor Profile • Whole blood sample for platelet count which at some sites may be part of a complete blood count with differential

* Based on the clinical evaluation of the suspected AESI (eg, whether thrombocytopenia is observed 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

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.

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

The investigator will be responsible for reporting cases of suspected child abuse or neglect according to local regulations.

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 and Assent Form

For adults:

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. 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.

For adolescents:

Legal guardian(s) (as defined in Section 2), as per local requirements must give written consent and the child (minor) must give assent according to local requirements after the nature of the study has been fully explained and before the child can be enrolled in the study. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants

7 years of age and older, depending on the institutional policies; it should be written in language appropriate to the child's developmental and functional status. Written assent should be obtained from participants who are able to write. A separate assent form written in language the participant can understand should be developed for adolescents. The participant (as appropriate) and legal guardian(s) 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/assent should be appropriately recorded by means of the participant's, if appropriate, and legal guardian's personally dated signature. After having obtained the ICF and assent form, a copy of each form must be given to the participant and to the participant's legal guardian(s). For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refer to the participants and his or her legal guardian(s) who have provided consent according to this process. Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate. Minor participants must be reconsented if they reach the age of majority during the course of the study, in order to continue participation. Emancipated minors may be permitted to enroll as allowed by local regulations.

The source document must include a statement that the consent signed by the legal guardian(s)and the assent signed by the participant (if appropriate) were obtained before the participant was enrolled in the study as well as the date the written consent was obtained. The authorized person obtaining the informed consent and assent must also sign the ICF and assent forms.

For adults and adolescents:

The ICF(s) and assent form must be signed before performance of any study-related activity. The ICF(s) and assent form 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 and assent form 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 or their legally acceptable representatives (in case of an adolescent participant, as appropriate) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. They 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 and legal guardian(s) (in case of an adolescent participant, as appropriate) are authorizing such access. It also denotes that the participant and legal guardian(s) agree to allow his or her study physician to recontact them for the purpose of obtaining consent for additional safety evaluations, if needed.

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

If the participant, if appropriate, or legal guardian(s) are unable to read or write, an impartial witness should be present for the entire informed consent and assent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant and legal guardian(s) (as appropriate for adolescents) 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/assent 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 intervention 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/assent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.3.6. Safety Monitoring Committees Structure

Safety Monitoring Committee

Initially, an internal DRC was commissioned for this study. Since then, an Independent Data Monitoring Committee (IDMC) was installed for the different studies throughout the COVID-19 vaccine program. In light of the transition of DRC to IDMC, when the term Safety Monitoring Committee (SMC) is mentioned, it can refer to either.

The SMC consists 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 SMC reviews data as indicated in Section 4.1, Overall Design. When appropriate, the conclusions of the SMC 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 6.10, Study Vaccination Pausing Rules, or at request of the sponsor's medical monitor or designee. The PI(s) and SRP will inform the SMC of any AE of concern.

The SMC reviews 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 SMC 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 SMC.

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

If any pausing rule is met (refer to Section 6.10) and, if following appropriate safety review it is deemed appropriate to restart dosing, the sponsor must submit a request to restart dosing with pertinent data to competent authority as a request for a substantial amendment, as required by local regulations or authority request (eg, the Medicines and Healthcare products Regulatory Agency [MHRA]). If needed, this will be followed by a substantial amendment of the IB and/or protocol.

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.

Statistical Support Group

The SSG is the statistical support group to the IDMC; they are provided with the statistical analysis data. As the IDMC, they are independent to the company.

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 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 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.

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

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

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

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility (including medical history and prestudy medication), and study identification; study discussion and date of signed informed consent/assent; 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. The

documentation of the positive RT-PCR result that serves as a trigger to start procedures for COVID-19 follow-up, will be considered source data.

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

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

10.3.11. Monitoring

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

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

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

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, 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 period if molecular testing indicates it is not a SARS-CoV-2 infection. If the molecular test is positive for SARS-CoV-2, the event should not be reported as an SAE. If molecular test results are not available within 24 hours of knowledge of the event, the event will be reported as an SAE, but will be subsequently downgraded from SAE status if it later turns out to be positive for SARS-CoV-2 by molecular testing.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.COV2.S, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to the 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 the version of September 2007[0], included in Section 10.6.

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. (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 vaccine in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study vaccine
- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study vaccine from breastfeeding

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

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccination, 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 (and semi-open-label) studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study vaccine, is considered an SAE.

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

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.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4.

Definition of Woman of Childbearing Potential

Woman of Childbearing Potential

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin an acceptable effective method of contraception, as described throughout the inclusion criteria.

10.6. 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).[0]

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
Creatine phosphokinase (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	1 - 10	11 – 50	> 50 and/or gross	Hospitalization or

high power field (rbc/hpf)			blood	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)

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

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

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** ☐ **forehead** ☐ **rectal**

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

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

- ☐ No Symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe

10.8. Appendix 8: Case Definitions for COVID-19

10.8.1. Case Definition for Moderate to Severe/Critical 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 until signs and symptoms disappear:

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

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

OR

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

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

* SpO2 criteria will be adjusted according to altitude per investigator judgment.
** Having 2 or more elements of a symptom (eg, vomiting and diarrhea or fatigue and loss of appetite) is counted only as 1 symptom for the case definition. To meet the case definition, a participant would need to have at least 2 different symptoms.

Case Definition for Severe/Critical COVID-19

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

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

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

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

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:

- 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

If a participant presents with symptoms as those listed by the US FDA harmonized case definition[0] (see Section 10.11), the investigator (or designated medically trained clinician) should assess if these are suggestive of COVID-19:

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample; **AND**
- COVID-19 symptoms consistent with those defined by the US FDA harmonized case definition[0] 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 fulfill the criteria for suspected COVID-19 based on **signs and symptoms** (see Section 8.1.2.1),

AND

- has a SARS-CoV-2 positive RT-PCR

OR

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

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

A positive RT-PCR for SARS-CoV-2 regardless of where the testing was performed (under the auspices of the study or through a private or public laboratory independent of the study) will need to be captured in the eCRF.

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

10.9. Appendix 9: Summary of Guidance from CDC Website[25] on Underlying Medical Conditions That Lead or Might Lead to Increased Risk for Severe Illness From COVID-19 – Used for Adult Cohort

People of any age with **certain underlying medical conditions** are at increased risk for severe illness from the virus that causes COVID-19. Severe illness from COVID-19 is defined as hospitalization, admission to the ICU, intubation or mechanical ventilation, or death.

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 but < 40 kg/m²)
- Severe Obesity (BMI ≥ 40 kg/m²)
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Pregnancy
- Sickle cell disease
- Smoking
- 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

[25] 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 03 December 2020.

- Neurologic conditions, such as dementia
- Liver disease
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

10.10. Appendix 10: Summary of Guidance from CDC Website[26] on Underlying Medical Conditions That Lead or Might Lead to Increased Risk for Severe Illness From COVID-19 – Used for Adolescent Cohort

CDC and partners are investigating a rare but serious medical condition associated with COVID-19 in children called Multisystem Inflammatory Syndrome in Children (MIS-C). We do not yet know what causes MIS-C and who is at increased risk for developing it.

Babies under 1 year old might be more likely to have severe illness from COVID-19. Other children, regardless of age, with the following underlying medical conditions might also be at increased risk of severe illness compared to other children:

- Asthma or chronic lung disease
- Diabetes
- Genetic, neurologic, or metabolic conditions
- Heart disease since birth
- Immunosuppression (weakened immune system due to certain medical conditions or being on medications that weaken the immune system)
- Medical complexity (children with multiple chronic conditions that affect many parts of the body who are often dependent on technology and other significant supports for daily life)
- Obesity

This list does not include every underlying condition that might increase the risk for severe illness in children. As more information becomes available, CDC will continue to update and share information about risk for severe illness among children.

[26] Source: https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html#:~:text=Babies%20under%201%20year%20old%20might%20be%20more%20likely%20to,Asthma%20or%20chronic%20lung%20disease. Accessed: 03 December 2020.

10.11. Appendix 11: 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 and were still accurate at the time of finalization of this protocol Amendment 2:

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.

10.12. Appendix 12: Multisystem Inflammatory Syndrome in Children

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C is a serious and potentially fatal condition that can arise in infants and children infected with SARS-CoV-2, and which can result in inflammation of a range of organs. Patients with MIS-C usually present with persistent fever, fatigue and a variety of signs and symptoms including multiorgan (eg, cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic) involvement, elevated inflammatory markers and, in severe cases, hypotension and shock.

MIS-C may present weeks after a child is infected with SARS-CoV-2. The child may have been infected from an asymptomatic contact and, in some cases, the infant and their parent(s)/caregiver(s) may not even know that they have been infected.

Although different presentations have been described, common symptoms include:

- Kawasaki disease-like features: conjunctivitis, red eyes; red or swollen hands and feet; rash; red cracked lips, swollen glands. Coronary artery enlargement and/or aneurysms have been described. Other symptoms include gastrointestinal (abdominal pain or diarrhea) and neurologic (headaches/meningitis) manifestations.
- Toxic shock syndrome-like features with hemodynamic instability.
- Cytokine storm/macrophage activation or hyperinflammatory features.
- Thrombosis, poor heart function, diarrhea and gastrointestinal symptoms, acute kidney injury.
- Shortness of breath suggestive of congestive heart failure.

The Center for Disease Control and Prevention issued a Health Advisory on 14 May 2020 that outlines the following case definition for MIS-C (https://www.cdc.gov/mis-c/hcp/index.html):

Case definition for MIS-C

- An individual aged <21 years presenting with fever[27], laboratory evidence of inflammation[28], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND

[27] *Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

[28] Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

Common Signs and Symptoms associated with MIS-C include the following:

- Fever (fever ≥38.0^{o}C for ≥24 hours, or report of subjective fever lasting ≥24 hours)
- Abdominal pain
- Vomiting
- Diarrhea
- Neck pain
- Rash
- Bloodshot eyes
- Feeling extra tired

Note: not all children will have the same signs and symptoms, and some children may have symptoms that are not listed here.

Immediate **emergency care** is required in the event of the child showing any of the following signs of MIS-C:

- Trouble breathing
- Pain or pressure in the chest that does not go away
- New confusion
- Inability to wake or stay awake
- Bluish lips or face
- Severe abdominal pain

Common laboratory findings include:

- An abnormal level of inflammatory markers in the blood, including elevated erythrocyte sediment rate (ESR)/C-reactive protein (CRP) and ferritin, lactate dehydrogenase (LDH).
- Lymphopenia <1000, thrombocytopenia <150,000, neutrophilia.
- Elevated B-type natriuretic peptide (BNP) or NT-proBNP (pro-BNP), hyponatremia, elevated D-dimers.

10.13. Appendix 13: TTS AESI Form

The form below represents the type of information that may be collected in case of a suspected AESI in order 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:

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)

[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

☐ 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		
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		
Anti-cardiolipin antibodies (IgG and IgM) or beta-2 glycoproteins antibodies		

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)
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		
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:

10.14. Appendix 14: Thrombotic Events to be Reported as Suspected AESIs

At the time of protocol Amendment 5 writing, the list of thrombotic events to be reported to the sponsor as suspected 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

10.15. Appendix 15: Protocol Amendment History

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

Amendment 5 (18 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.

The purpose of this amendment is to update safety procedures for all enrolled participants (adults and adolescents). At the time of protocol Amendment 5, enrollment and vaccination of adolescents is paused pending further evaluation of benefit-risk in adolescents. Enrollment and vaccination of adolescents will resume with protocol Amendment 6.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults$ 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 1.3.4 Active Vaccine Regimen: Placebo Groups 6, 8 and 10 (28-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.5 Groups A to F (56-day interval [2-dose and 1- dose regimens, with booster]) – Adolescents 1.3.8 Participants with a Suspected AESI – Adults & Adolescents 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 6.9 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.4 Hematology Clinical Laboratory Assessments 8.3 Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, and Other Safety Reporting 8.3.1 Time Period and Frequency for Collecting Adverse Event, Adverse Event of Special Interest,	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 TTS, with onset of symptoms approximately 1-2 weeks after vaccination. Therefore, additional reporting and data collection procedures are implemented to follow-up thrombotic events and thrombocytopenia and identify cases of TTS.

Section Number and Name	Description of Change	Brief Rationale
and Serious Adverse Event Information 8.3.2 Method of Detecting Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events 8.3.3 Follow-up of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events 8.3.6 Adverse Events of Special Interest 8.3.6.1 Thrombosis with Thrombocytopenia Syndrome 9.4.2 Primary/Secondary Endpoints 10.2 Appendix 2: Hematology Clinical Laboratory Tests 10.3.6 Safety Monitoring Committees Structure 10.4 Appendix 4: Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 10.4.5 Procedures 10.13 Appendix 13: TTS AESI Form (added) 10.14 Thrombotic Events to be Reported as Suspected AESIs (added)		
1.1 Synopsis 1.2 Schema 1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 4.1 Overall Design 6.4 Unblinding and Open-label Phase (added) 8 STUDY ASSESSMENTS AND PROCEDURES 9.4.1 General Considerations	Text/tables were updated to indicate that all adult groups received injection 3, either antigen presentation (Group 1-5, 7, 9) or placebo (Groups 6, 8, 10), followed by an on-site unblinding visit between Injection 3 and 6 months post Injection 3. Due to a second study pause in April 2021, no groups will have been unblinded on a group level prior to implementation of protocol Amendment 5. Unblinding visit was added to Figures 1, 2 and 3.	To reflect what actually occurred during the study.
1.1 Synopsis 4.1 Overall Design 4.3 Justification for Dose	Justification for the 2-dose regimen in adult participants who originally received placebo was added.	the total number of placebo recipients from Groups 6, 8 and 10 (target n=75) is intended to fulfill the original target enrollment for Group 7, which was meant to receive 2 doses at a 28-day interval.

Section Number and Name	Description of Change	Brief Rationale
1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 8 STUDY ASSESSMENTS AND PROCEDURES	Additional 5 mL blood draw for plasma at Visit 10 is deleted.	All participants received Injection 3 prior to implementation of protocol Amendment 4, so this draw was not collected from any participants.
1.1 Synopsis 1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 1.3.4 Active Vaccine Regimen: Placebo Groups 6, 8 and 10 (28-day interval schedule [2-dose and single dose regimens]) – Adults 3 OBJECTIVES AND ENDPOINTS 8.2.4 Hematology Clinical Laboratory Assessments 10.2 Appendix 2: Hematology Clinical Laboratory Tests	Anti-PF4 was added as a hematology endpoint.	This was added to fully evaluate coagulation parameters per current medical practice
1.1 Synopsis 1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 6.4 Unblinding and Open-label Phase 9.4.1 General Considerations	Reference to EUA or other approval and reference to “at approximately 6 months of study participation” were deleted in the adult sections, and unblinding procedures were instead linked to implementation of Amendment 5.	Clarification of timing around unblinding
1.2 Schema 1.3.4 Active Vaccine Regimen: Placebo Groups 6, 8 and 10 (28-day interval schedule [2-dose and single dose regimens]) – Adults 8 STUDY ASSESSMENTS AND PROCEDURES	The Visits were renumbered in Figure 4 and SoA for Placebo Groups to clarify that the start of the open-label portion of the study from the time of unblinding and subsequent visits are not linked to prior vaccinations.	Clarification of changes made in protocol Amendment 4.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 6.4 Unblinding and Open-label phase 6.7 Continued Access to Study Vaccine After the End of the Study 7.1 Discontinuation of Study Vaccination 9.5 Planned Analysis	Text was modified to indicate that participants who were already unblinded for any reason may receive Ad26.COV2.S vaccine upon discussion with the investigator, provided that they did not receive another COVID-19 vaccine.	Since all participants will now be unblinded, it is permissible for those who were previously unblinded but who have not been vaccinated with another COVID-19 vaccine to be offered Ad26.COV2.S.
1.1 Synopsis 4.1 Overall Design 10.3.6 Safety Monitoring Committees Structure	The text regarding the Safety Monitoring Committees (SMC) was streamlined and updated to reflect the installation of the IDMC for VAC31518COV2001.	Update
4.1 Overall Design 4.4 End of Study Definition	Study duration/end of study definition was corrected based on the Schedule of Activities.	Correction
2.3.1 Risks Related to Study Participation	It has been clarified that anaphylaxis is considered an important identified risk.	To align with the vaccine's identified risks.
5.2.1 Exclusion Criteria for Adults	Exclusion criterion is reinstated to exclude participation by employees of the sponsor or the study sites and their family members.	Reinstatement per health authority request.
6.4 Unblinding and Open-label Phase	Section was added to indicate what procedures should be followed around unblinding.	Clarification
7.1 Discontinuation of Study Vaccination	Text was modified to indicate that discontinuation of study vaccination for a positive test result for SARS-CoV-2 infection is only applicable for the double-blind phase.	At the time of protocol Amendment 5, all adult participants had received Injection 3. Following unblinding, all placebo participants will be offered a 2-dose (28-day interval) Ad26.COV2.S vaccination regimen at the $5x10^{10}$ vp dose level.
1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 1.3.4 Active Vaccine Regimen: Placebo Groups 6, 8 and 10 (28-day interval schedule [2-dose and single dose regimens]) – Adults 4.1 Overall Design 8 STUDY ASSESSMENTS AND PROCEDURES	Total blood volumes to be drawn were updated to align with changes in Section 1.3.	Update/alignment
1.3.7 Procedures for Participants With (Suspected) COVID-19 – Adults and Adolescents 8.1.2 Procedures in Case of (Suspected) COVID-19	Schedule/text was clarified to indicate that nasal swabs should be performed twice weekly or more often from Day 3 of COVID-19 episode until resolution.	Clarification

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. A statement was added to the adolescent portions to indicate that enrollment and vaccination of adolescents is paused pending further evaluation of the risk-benefit in adolescents.	Minor errors were noted Emphasis that the adolescent portions of the protocol should not be followed; they will be updated with Amendment 6, at which time adolescent vaccinations may resume.

Amendment 4 (04 March 2021)

Overall Rationale for the Amendment: In this amendment, the adolescent participants will be stratified by age into 2 groups (16 to 17 years of age, inclusive and 12 to 15 years of age, inclusive). A staggered approach will be implemented, with the initial safety assessments conducted in the older adolescents (16 to 17 years of age) and limited to 11 sentinels. Tolerability to the Ad26.COV2.S vaccine at the $2.5x10^{10}$ virus particle (vp) dose level will initially be evaluated at Day 4 (3 days post-vaccination) by the Safety Monitoring Committee (SMC), with further safety assessments conducted in a safety cohort of 22 participants at Day 8 (7 days post-vaccination). If the safety and reactogenicity profile is acceptable within the 16-17 years age group, then the $2.5x10^{10}$ vp dose level will be assessed as described above in adolescents at 12 to 15 years of age, inclusive. Similarly, the safety and reactogenicity profile of the Ad26.COV2.S ($5x10^{10}$ vp) dose level, that has been shown to be safe and efficacious in adults (≥18 years of age) will be assessed within adolescents at 16-17 years of age, before proceeding to the younger age group and full enrollment of adolescent participants.

Adolescents who were initially assigned to receive a single dose of Ad26.COV2.S at 2.5 10^{10} vp, will now receive 2 doses of Ad26.COV2.S at $2.5x10^{10}$ (56-day interval), as a single dose at $2.5x10^{10}$ may provide suboptimal protection. Adolescents in Groups A and B will now receive the same dose of active vaccine. Group naming has been retained to facilitate the transition of participants enrolled under the previous protocol amendment.

In addition, this amendment outlines procedures to be followed after Emergency Use Authorization (EUA), or similar program/authorization or approval, or approval in any country for both the Ad26.COV2.S vaccine and the current protocol Amendment 4 by both health authority and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) have been obtained, where a single dose of Ad26.COV2.S will be offered to enrolled participants who initially received placebo, resulting in de facto unblinding of participants and investigators.

Section number and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis; Section 4.1. Overall Design; Section 6.3. Measures to Minimize Bias: Randomization and Blinding; Section 8.1.1. Immunogenicity Assessments; Section 9.1. Statistical Hypotheses; Section 9.2.1. Immunogenicity;	Randomization of adolescent participants will be stratified by study site and age group (half of the participants 12 to 15 years of age, inclusive, and half of the participants 16 to 17 years of age, inclusive). Enrollment will progress in parallel, with the safety profile of the Ad26.COV.2 vaccine doses ($2.5x10^{10}$ vp and $5x10^{10}$ vp dose levels) in adolescents assessed separately by age group.	The Adolescent group will be split into 2 groups based on age (12 to 15 years, inclusive and 16 to 17 years of age, inclusive) for the purpose of randomization and stratification. The purpose of this staggered and age-stratified approach is to collect safety data on adolescent participants 16 to 17 years of age at the $2.5x10^{10}$ vp dose level, prior to

Section number and Name	Description of Change	Brief Rationale
Section 9.3 Populations for Analysis Sets; Section 9.5 Planned Analysis	This is reflected in the revised sections on Statistical Analysis, including Table 10.	proceeding to the younger adolescent cohort and/or to the higher dose level of $5x10^{10}$ vp.
Section 1.1. Synopsis; Section 1.2. Schema; Section 1.3.1. Schedule of Activities (SoA): Adult Groups 1 to 6; Section 1.3.2. SoA Adult Groups 7 and 8; Section 1.3.3. SoA Adult Groups 9 and 10; Section 1.3.4. SoA Active Vaccination Regimen: Adult Placebo Groups 6, 8 and 10; Section 1.3.5. SoA Adolescent Groups A to F; Section 1.3.4. SoA Active Vaccination Regimen: Placebo Group 10; 4.1. Overall Design; Section 6.3. Measures to Minimize Bias: Randomization and Blinding; Section 6.7 Continued Access to Study vaccine After the End of the Study Section 8 Study Assessments and Procedures.	Once Emergency Use Authorization (EUA), or similar program/authorization or approval, or approval in any country for both the Ad26.COV2.S vaccine and the current protocol Amendment 4 by both Health Authority and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) have been obtained, all study participants and investigators will be partially unblinded (informed whether they received placebo or Ad26.COV2.S) and the study will continue as a (semi) open-label study. - At approximately 6 months of study participation, adult participants who were initially enrolled to receive placebo (Groups 6, 8 and 10), will be offered a 2-dose (28-day interval) Ad26.COV2.S vaccination regimen at the $5x10^{10}$ vp dose level. The time point at which adult participants reach approximately 6 months of study participation is independent of the 3rd vaccination, therefore participants may or may not have already received the 3rd vaccination by the time of unblinding. At approximately 6 months of study participation or on receipt of EUA, or similar program/authorization or approval, or approval in any country for both the Ad26.COV2.S vaccine and the current protocol Amendment 4 by both Health Authority and IEC/IRB have been obtained, all adolescent participants will be unblinded to the primary vaccination regimen. Participants who were initially enrolled to receive placebo (Groups C and F), will be offered a 2-dose (56-day interval) Ad26.COV2.S vaccination regimen at the 2.5 $x10^{10}$ vp and $5x10^{10}$ vp dose level, respectively.	- As the vaccine is highly efficacious against severe disease, hospitalization, and death, it is considered ethical to offer the active vaccine to the adult and adolescent placebo controls in this study. An unblinding visit will be scheduled to inform all participants about their study vaccine allocation, as well as to offer all placebo recipients Ad26.COV2.S after EUA, or similar program/authorization or approval, or approval in any country for both the Ad26.COV2.S vaccine and the current protocol Amendment 4 by both Health Authority and IEC/ IRB. - The 6 Month visit with a broadened visit window will be used as an unblinding visit to allow for rapid crossover in the context of logistic issues. Investigators will be encouraged to follow health authority guidelines on prioritization of immunization when feasible.
Section 1.1. Synopsis; Section 4.1. Overall Design	The following statement has been added: Countries may participate in the adult and adolescent portions of the study or they may participate in either the adult or adolescent portion.	Clarification

Section number and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis; Section 9.5. Planned Analysis	Adult Participants: The primary analysis will include safety and immunogenicity data (VNA and ELISA) for all participants through Day 85 (Groups 1-6), Day 57 (Groups 7-8) or Day 113 (Groups 9-10). Adolescent Participants: Interim analysis will be performed once 250 participants in the 16-17 years of age group (including all adolescents in Group A-C receiving the $2.5x10^{10}$ dose [n=75] plus placebo controls, and a substantial proportion of participants [n ≥125] in Groups D-F receiving the $5x10^{10}$ dose) have reached the Day 28 post-dose 1 time point. Unblinded data at the vaccination group level will be available to the sponsor and might be used for regulatory submissions. A separate interim analysis of safety and immunogenicity will be performed for all groups in the adolescent cohort (Groups A-C and D-F) to include both the 12-15 years and 16-17 years age groups, and will include 28-day immunogenicity (ie, the 1-dose non-inferiority comparisons) and 28-day safety data post-dose 1 of all groups in the adolescent cohort. The sponsor will be unblinded, 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 until the end of study.	Updates to the interim and primary analysis for both adult and adolescent participants to reflect the changes in study design.
Section 1.1. Synopsis; Section 4.1. Overall Design; Section 8.3.2. Method of Detecting Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events Information	Addition of the following statement: After each vaccination, all participants will remain under observation at the study site for at least 1 hour (including participants in the Sentinel and Safety Cohort) to monitor for the presence of any acute reactions and solicited events.	Clarification and alignment.
Section1.1. Synopsis, Section 3. Objectives and Endpoints; Section 4.1. Overall Design; Section 8.1.1 Immunogenic Assessments; Section 8.1.2. Procedures in case of (Suspected) COVID-19	Endpoint Analysis: - Serological response to vaccination as measured by virus neutralization assay (VNA) titers and enzyme-linked immunosorbent assay (S-ELISA, ELISA Units/mL [EU/mL]), 28 days after Vaccination 2.	Updated to reflect the inclusion of the virus neutralization assay in analysis of serological responses to vaccination (in addition to the use of the enzyme-linked immunosorbent assay).

Section number and Name	Description of Change	Brief Rationale
	- Antibody geometric mean titers (GMTs) (VNA) and geometric mean concentrations (GMCs) (S-ELISA), 28 days after Vaccination 2.	
Section 5.2.1. Exclusion Criteria for Adults; Section 5.2.2. Exclusion Criteria for Adolescents	Adolescents: - Exclusion criterion 15 modified to specify drug abuse. - Exclusion criterion 21 added to clarify that participants with a history of Kawasaki disease will be excluded. - Exclusion criterion 22 added to clarify that participants with a history of an underlying clinically significant acute or chronic medical condition or physical examination findings may be excluded as per Investigator's judgment. Adults and Adolescents: Exclusion criteria 13 and 14, respectively, deleted: There is no restriction on enrollment of participants that are employees of the investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.	- Alignment of exclusion criteria in adult and adolescent participants. - Notably, exclusion of participants with a history of Kawasaki disease, is applicable to adolescent participants, only.
Section 1.1. Synopsis; Section 1.3.7 Schedule of Activities: Procedures for Participants With (Suspected) COVID-19; Section 8.1.2. Procedures in case of (suspected) COVID-19	The following text has been revised to clarify that the sponsor recommends to follow-up on participants with suspected COVID-19 until 2 consecutive SARS-CoV-2 negative nasal swabs could be obtained.	Clarification of procedures in case of suspected COVID-19 infection.
Throughout the protocol (naming of adolescent study groups)	Groups A and B will be receiving the same vaccination regimen consisting of 2 doses of Ad26.COV2.S at $2.5x10^{10}$ vp.	Group naming has been retained in protocol Amendment 4 to align with protocol Amendment 2 and to allow for transition from one amendment to the next with the same flow of participants in the sentinel and safety cohorts.
Section 1.1. Synopsis; Section 1.3. Schedule of Activities; Section 4.1. Overall Design; Section 9.5. Planned Analysis Throughout the protocol (numbering of adult study groups)	The 2 additional adult Groups 11 and 12 that were added in the previous protocol Amendment 3 have been removed. The overall total number of adult participants to be enrolled will revert to the original planned enrollment of 550 participants.	The original intention in adding Groups 11 and 12 was to ensure that the vaccination regimen (28-day interval) originally intended for Groups 7 and 8 prior to the study pause in October 2020 were covered. The vaccination regimen (2 doses of Ad26.CoV2.S at $5x10^{10}$ administered at a 28-day interval) is now covered by cross-vaccination of the participants that originally received placebo in the primary vaccine regimen in Groups 6, 8 and 10.

Section number and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis; Section 3. Objectives and Endpoints; Section 8.1.1. Immunogenicity Assessments	Use of the Enzyme-linked Immunospot (ELISpot) assay to measure cellular immunogenicity elicited by vaccination has been removed as an endpoint from the exploratory objectives. Table 8: Summary of Humoral and cellular Immunogenicity Assays has been updated to reflect this.	Use of ELISpot assay removed.
Section 1.1. Synopsis; Section 3. Objectives and Endpoints; 8.1.1. Immunogenicity Assessments	The following Exploratory Endpoints have been added to the exploratory objectives: - To further assess the humoral immune response to Ad26.COV2.S: Analysis of neutralizing antibodies against emerging SARS-CoV-2 variants. - To further assess humoral immune responses generated by the Ad26.COV2.S vaccine using data obtained from cohorts of young participants (≥18 to ≤25 years of age, inclusive) in the sponsor's clinical program.	- To increase understanding of the protective immunity conferred by the Ad26.COV2.S vaccine to emerging SARS-CoV-2 variants in young adults and adolescents. - To increase the power of the statistical analysis performed by comparing the humoral immune responses generated by the Ad26.COV2.S vaccine in young participants (≥18 to ≤25 years of age, inclusive) across the various clinical studies conducted by the sponsor.
Section 6.10. Study Vaccination Pausing Rules Section 10.3.6. Safety Monitoring Committee Structure	Text added, stating that the study vaccination pausing rules apply to "adolescent participants only". Text added stating that: "If any pausing rule is met and, if following appropriate safety review it is deemed appropriate to restart dosing, the sponsor must submit a request to restart dosing with pertinent data to competent authority as a request for a substantial amendment, as required by local regulations or authority request.".	Clarification that the study vaccination pausing rules applies to adolescent participants only. Clarification of the procedures to be followed in the event a pausing rule is met; notably that the sponsor must submit a request to restart dosing to the appropriate authorities.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 3 (22 December 2020)

Overall Rationale for the Amendment: In October 2020, the current study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2, rendering the intent of the 28-day vaccination interval in these groups futile (see Table 2). Efforts will be made to vaccinate these participants, preferably in a 56-day vaccination interval. In this amendment, 2 additional groups (Groups 11 and 12) have been added to determine to evaluate whether a 28-day interval between Vaccination 1 and Vaccination 2 is acceptable. Groups 11 and 12 will have the same vaccination regimen as originally intended for Groups 7 and 8 prior to the pause. Given the lack of sensitivity of the psVNA, and the high correlation between the wtVNA and ELISA assays and high throughput of the ELISA assay, the ELISA has been selected for the non-inferiority (NI) primary endpoint for the comparison of the humoral responses between adults and adolescents. Procedures to be followed in the event that an investigator receives a request to unblind study participants who may become eligible to receive an authorized/licensed COVID-19

vaccine when these become available have been added. This amendment also describes that if a correlate or threshold for protection against COVID-19 is established in terms of humoral immunity, then a statistical comparison to that correlate or threshold will substitute non-inferiority testing to immune responses to vaccine at release.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 1.3.2 Groups 7, 8, 11 and 12 (28-day interval schedule)-Adults 4.1 Overall Design 4.4 End of Study Definition 6.1 Study Vaccinations Administered 8 STUDY ASSESSMENTS AND PROCEDURES 9.5 Planned Analysis	Two additional groups (Groups 11 and 12) have been added that will have the same vaccination regimen as originally intended for Groups 7 and 8 prior to the study pause in October 2020.	To evaluate a 28-day interval between Vaccination 1 and Vaccination 2.
1.1 Synopsis 3 Objectives and Endpoints 9.4.2 Primary/Secondary Endpoints	psVNA has been replaced by ELISA from the NI endpoints between adults and adolescents.	Several psVNAs have been evaluated by the sponsor, and this evaluation showed that these assays have a lack of sensitivity in comparison to the wtVNA. The ELISA and wtVNA show a high correlation across different age groups and timepoints. The use of the ELISA has therefore been selected for the non-inferiority primary endpoints comparing the humoral responses of adults and adolescents.
1.1 Synopsis 3 Objectives and Endpoints	The option of the VNA assay has been removed in the primary endpoints for the adults.	The ELISA will be the assay used for the primary endpoints.
1.1 Synopsis 3 Objectives and Endpoints	Description of the correlate or threshold of protection against COVID-19 if established in terms of humoral immunity has been added.	A correlate or threshold of protection will be a better indication of efficacy.
1.1 Synopsis 3 Objectives and Endpoints	Addition of an exploratory 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) Addition of one exploratory objective/endpoint: To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	 For in-depth analysis of the binding antibody generated by Ad26.COV2.S To further confirm the correlation between ELISA and wtVNA in different age groups and timepoints and confirm the choice of the ELISA as primary endpoint in the

Section number and Name	Description of Change	Brief Rationale
		NI objectives comparing immunogenicity of adults and adolescents.
1.1 Synopsis 8.1.1 Immunogenicity Assessments	Addition of the MSD assay.	For in-depth analysis of the binding antibody generated by Ad26.COV2.S
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 7.1 Discontinuation of Study Vaccination 6.7 Continued Access to Study Vaccine After the End of the Study 9.5 Planned Analysis	Clarification of procedures for unblinding of study participants who may become eligible to receive an authorized/licensed COVID-19 vaccine during the course of the study.	To ensure that if participants become eligible to receive an authorized/licensed COVID-19 vaccine, they are aware of the potential options and ramifications, including the lack of safety data on receiving 2 different COVID-19 vaccines.
1.3 Schedule of Activities 8.2.4 Hematology Clinical Laboratory Assessments	Clarification that upon implementation of this amendment blood draws for hematology assays will be plasma.	It was confirmed that D-dimers and Lupus anticoagulant tests cannot be performed in serum. Therefore, previously collected serum samples will not be adequate for these tests. Plasma samples will be collected for the purpose of these testing in all groups once protocol Amendment 3 is approved and implemented.
5.1.2 Inclusion Criteria for Adolescents (12-17 years inclusive)	Modified inclusion criteria so that a participant or parent/legal guardian could sign the ICF, participate in all procedures/visits and provide verifiable identification.	In certain countries adolescent participants who are 16 and 17 years of age are treated as adults in clinical trials.
5.2.1 Exclusion Criteria for Adults (18-55, Inclusive and 65 Years and Older) 6.9 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination	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
5.2.1 Exclusion Criteria for Adults (18-55, Inclusive and 65 Years and Older) 6.9 Prestudy and Concomitant Therapy	Clarified that investigational drug includes drugs for prophylaxis of COVID-19. Also 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.
5.2.2 Exclusion Criteria for Adolescents (12-17 Years, Inclusive)	Clarified that investigational drug includes drugs for prophylaxis of COVID-19.	Alignment with Phase 3 protocols.
5.2.1 Exclusion Criteria for Adults (18-55, Inclusive and 65 Years and Older)	Updated the list of conditions that increase the risk of progression to severe COVID-19.	Alignment with Phase 3 protocols.

Section number and Name	Description of Change	Brief Rationale
5.2.1 Exclusion Criteria for Adults (18-55, Inclusive and 65 Years and Older)	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.
1.1 Synopsis 3 Objectives and Endpoints 8.1.2.1 Prespecified Criteria for (Suspected) COVID-19 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 9.4.2 Primary/Secondary Endpoints 10.12 Appendix 12: Multisystem Inflammatory Syndrome in Children	Addition of multisystem inflammatory syndrome in children as an SAE. Description of the syndrome and common signs has been added as an appendix.	Alignment with Phase 3 pediatric study protocols
1.3 Schedule of Activities 7.1 Discontinuation of Study Vaccination 7.2 Participant Discontinuation/Withdrawal from the Study	Clarified that participants who discontinue 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.
6.3 Measure 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
9.5 Planned Analysis	Additional wording added to explain the investigator or sponsor may have to be unblinded due to unexpected events.	Clarification
6.8 Treatment of Overdose	Definition of what can be regarded as an overdose was corrected.	Correction of inconsistency.
8.1.2 Procedures in Case of (Suspected) COVID-19	Clarification that additional swabs should be taken by a healthcare professional from the participant as soon as possible, but with a minimum of 1 day between the swabs.	Clarification
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 judgment.	Clarification
1.1 Synopsis 9.2.1 Immunogenicity	Standard deviations have been updated for NI in the statistical sections.	Per endpoint update
6.10 Study Vaccination Pausing Rules 10.3.6 Safety Monitoring Committees Structure	Text was added to clarify that if there will be any study pause, the sponsor will submit a request to restart the study with pertinent data to the Health Authorities as a request for a substantial amendment, as required by the local regulations.	Upon Health Authority feedback
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 2 (29 October 2020)

Overall Rationale for the Amendment: In this amendment, adolescents (aged 12 to 17 years, inclusive) are included in the study to demonstrate non-inferiority of the immune responses in adolescents (5x1010 and 2.5x1010 vp dose levels, 1- and 2-dose regimens) to the immune responses of adults in this COV2001 study (5x1010 vp dose levels, 1- and 2-dose regimens). The 5x1010 vp dose level is the one being used in the Phase 3 efficacy studies COV3001 (1-dose regimen) and COV3009 (2-dose regimen).

The mitigation strategy after a study pause is clarified.

In October 2020, the current study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2 (Visit 4), rendering the intent of the 28-day vaccination interval in these groups futile. It is explained that efforts will be made to vaccinate these participants, preferably in a 56-day vaccination interval.

Upon request of the CCMO (Centrale Commissie Mensgebonden Onderzoek) in The Netherlands, hematology laboratory tests have been added to assess potential vaccine-induced anti-phospholipid syndrome and potential vaccine-induced activation of coagulation.

Additional changes are listed below.

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

Section Number and Name	Description of Change	Brief Rationale
1 PROTOCOL SUMMARY (and subsections) 2 INTRODUCTION 2.1 Study Rationale 2.2 Background 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4 STUDY DESIGN (and subsections) 5 STUDY POPULATION 5.1 Inclusion Criteria (and subsections) 5.2 Exclusion Criteria (and subsections) 5.4 Screen Failures 6.1 Study Vaccinations Administered 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Dose Modification 7.1 Discontinuation of Study Vaccination 7.2 Participant Discontinuation/Withdrawal From the Study (and subsection) 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.1 Immunogenicity Assessments 8.1.3 Asymptomatic SARS-CoV-2 Infection 8.2.3 Pregnancy Testing	Inclusion of adolescents (aged 12 to 17 years, inclusive) in the study. Blood volumes to be collected have been adapted according to the population and are reduced versus the adult cohorts.	To demonstrate non-inferiority to adult results (in Phase 3) by immunobridging

Section Number and Name	Description of Change	Brief Rationale
8.3.2 Method of Detecting Adverse Events, and Serious Adverse Events 9.1 Statistical Hypotheses 9.2 Sample Size Determination (and subsections) 9.4.2 Primary/Secondary Endpoints 9.5 Planned Analysis 10.1 Appendix 1: Abbreviations 10.3.1 Regulatory and Ethical Considerations 10.3.3 Informed Consent Process and Assent Form 10.3.4 Data Protection 10.3.5 Long-Term Retention of Samples for Additional Future Research 10.3.10 Source Documents 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 – Used for Adolescent Cohort 11 REFERENCES		
1.1 Synopsis 6.1 Study Vaccinations Administered 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 In October 2020, the current study was temporarily paused because one of the pausing rules was met in study COV3001. When the pause was lifted, most of the participants in Groups 7-8 had missed their visit window for Vaccination 2 (Visit 4), rendering the intent of the 28-day vaccination interval in these groups futile. As the actual vaccination might coincide with the intervals from other groups, it might be possible to use the data according to that interval.
1.1 Synopsis 9.5 Planned Analysis	Clarified that all available data will be included in the interim analysis of the adult cohort.	Mitigation in case of study pause: Clarification which data will be included.
6.10 Study Vaccination Pausing Rules	Text adapted to state that this study will also be paused if a pausing rule is met in study COV1002 or COV3001.	Mitigation in case of study pause: Additional safety measure
1.1 Synopsis 1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults	Addition of hematology clinical laboratory assessments for adults.	Upon request of CCMO in The Netherlands, to assess potential vaccine-induced antiphospholipid syndrome and potential

Section Number and Name	Description of Change	Brief Rationale
1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.4 Hematology Clinical Laboratory Assessments 10.2 Appendix 2: Hematology Clinical Laboratory Tests		vaccine-induced activation of coagulation
1.1 Synopsis 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 4.1 Overall Design 6.10 Study Vaccination Pausing Rules 8.2 Safety Assessments 9.5 Planned Analysis 10.1 Appendix 1: Abbreviations 10.3.6 Safety Monitoring Committees Structure	Explanation added that IDMC will take over responsibilities of DRC.	Initially, an internal DRC was commissioned for this study. However, an Independent Data Monitoring Committee (IDMC) will be installed for the different studies throughout the COVID-19 vaccine program. Once this is in place, this IDMC will, after a transition period, take over the responsibilities of the DRC in this study.
1.1 Synopsis 1.3 Schedule of Activities (SoA) (and subsections) 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 8.1.2 Procedures in Case of (Suspected) COVID-19 (and subsection) 8.1.3 Asymptomatic SARS-CoV-2 Infection 10.3.10 Source Documents 10.8.4 Case Definition for Asymptomatic or Undetected COVID-19	An RT-PCR positive finding for SARS-CoV-2 from any source (within or outside the study), even if asymptomatic, will be considered as a prespecified criterion for (suspected) COVID-19 and will therefore trigger follow-up as described in Section 1.3.7. In addition, any (suspected) COVID-19 case (Section 1.3.7) will be followed until resolution of symptoms AND until 2 consecutive SARS-CoV-2 negative swabs are available.	To ensure safety of staff and other persons coming in contact with the infected participant.
1.1 Synopsis 1.3.8 Procedures for Participants With (Suspected) COVID-19 – Adults and Adolescents 4.1 Overall Design 8.1.2 Procedures in Case of (Suspected) COVID-19 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 judgment 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	Vaccination with Ad26.COV2.S may

Section Number and Name	Description of Change	Brief Rationale
	discouraged and if testing would be needed, the site will guide the participant to an appropriate assay.	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.
2.3.1 Risks Related to Study Participation 9.5 Planned Analysis	Clarified that selected members of the statistical programming and statistics group will receive individual level unblinded data, when unblinding at the participant level is required.	Alignment with other studies of the program
2.3.1 Risks Related to Study Participation 6.9 Prestudy and Concomitant Therapy	Guidance on the use of antipyretics during the study has been clarified.	To clarify that antipyretics are recommended post-vaccination for symptom relief, as needed. Prophylactic antipyretic use is not encouraged.
2 INTRODUCTION 2.2 Background 2.3.1 Risks Related to Study Participation	Recent data from the first-in-human study COV1001 have been added and background information on COVID-19 and information on non-COVID-19 Ad26-based vaccines has been updated where relevant.	Alignment and transparency
5.2.1 Exclusion Criteria for Adults (18-55 years, Inclusive and 65 Years or Older) 6.7 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 program.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.1.1 Immunogenicity Assessments	Addition of 2 exploratory humoral immunogenicity endpoints: Functional and molecular antibody characterization and passive transfer.	For analysis of antibody characteristics and analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 8 STUDY ASSESSMENTS AND PROCEDURES	Blood volume of SARS-CoV-2 serological test added.	correction

Section Number and Name	Description of Change	Brief Rationale
1.3.8 Procedures for Participants With (Suspected) COVID-19 – Adults and Adolescents 8 STUDY ASSESSMENTS AND PROCEDURES 8.5 Biomarkers	Clarified that humoral immunity and PAXgene sample is also to be taken at COVID-19 Day 3-8. Blood volume added.	correction
1.1 Synopsis 1.3.8 Procedures for Participants With (Suspected) COVID-19 – Adults and Adolescents 8.1.2 Procedures in Case of (Suspected) COVID-19	Physical examination and vital signs assessment added to COVID-19 Days 3-8.	Alignment with Phase 3 program.
1.3.1 Groups 1 to 6 (56-day interval schedule [2-dose and single dose regimens]) – Adults 1.3.2 Groups 7 and 8 (28-day interval schedule)- Adults 1.3.3 Groups 9 and 10 (84-day interval schedule) – Adults 8.2.2 Vital Signs	Vital signs assessment are recommended before blood sampling. This instruction has been made consistent throughout the document.	Consistency throughout document
9.4.2 Primary/Secondary 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 and that in general, (S)AEs caused by SARS-CoV-2 will also be removed and presented separately.	Clarification on criteria and analysis of (S)AEs have been made.
10.3.10 Source Documents	It has been clarified that source documents for medical history and prestudy therapies determining eligibility of the participants needs to be collected.	To ensure that all necessary information to properly assess SAEs (relatedness) is collected.
Title page	Prepared by line removed.	To align with internal guidelines on legal entity to be mentioned on title page
Throughout the protocol	Minor errors and inconsistencies were corrected throughout the protocol.	Correction of minor errors and inconsistencies

Amendment 1 (21 August 2020)

Overall Rationale for the Amendment: In this amendment, a more flexible window is allowed between molecular test for SARS-CoV-2 infection and vaccination and a clarification is added to the eligibility criteria on blood pressure for participants ≥65 years of age. In addition, other changes have been made for alignment with other study protocols within the program.

Section Number and Name	Description of Change	Brief Rationale
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.	Operational request
1.1 Synopsis 1.3 Schedule of Activities, 4.1 Overall Design 8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms	Clarified that the nasal swab is preferably to be taken by the caregiver (spouse, partner, relative, friend, or health care professional).	Operational request
5.1 Inclusion Criteria, 5.2 Exclusion Criteria	Clarification added to the eligibility criteria on blood pressure for participants aged 65 years and older.	Alignment within the program
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	Clarified that the use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination and during the study.	Alignment within the program, based on National Institute of Allergy and Infectious Diseases (NIAID) Prevention Science Review Committee (PSRC) feedback
5.2 Exclusion Criteria	It has been clarified that every effort will be made to avoid inclusion of participants who have been previously enrolled in coronavirus studies and to prevent subsequent enrollment of a participant in other coronavirus studies during their participation in this study.	Based on NIAID PSRC feedback
5.2 Exclusion Criteria	It has been clarified that planning to become pregnant within 3 months after study vaccine is an exclusion criterion.	Alignment within the program, based on NIAID PSRC feedback
6.8 Prestudy and Concomitant Therapy	A clarification has been made regarding the use of analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs.	Alignment within the program
8 Study Assessments and Procedures	Added that all participants will be counseled on COVID-19 prevention each time that they have a contact with study site staff in line with local guidelines.	Clarification and alignment within the program
8.1.2.1 Prespecified Criteria for Suspected COVID-19	Changed “new loss of taste or smell” to “new or changing olfactory or taste disorders”.	To align wording across all case definitions
10.7.1 Case Definition for Moderate to Severe COVID-19 10.7.2 Case Definition for Mild COVID-19	The case definitions of both mild and moderate COVID-19 have been modified.	Based on FDA and NIAID PSRC feedback to simplify the case definitions
1.3.5 Procedures for Participants With COVID-19-like Signs and Symptoms	Clarified that a participant will be notified of a confirmed positive SARS-CoV-2 infection.	Alignment within the program, based on NIAID PSRC feedback

Section Number and Name	Description of Change	Brief Rationale
8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms		
8.1.2 Procedures in Case of COVID-19-like Signs and Symptoms	Clarified that study staff visiting participants at home will use personal protective equipment according to local regulations.	Alignment within the program, based on NIAID PSRC feedback
Throughout the protocol	Minor errors and inconsistencies were corrected throughout the protocol.	Correction of minor errors and inconsistencies

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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): Javier Ruiz Guiñazú, MD

Institution: Janssen Vaccines & Prevention B.V.

Signature: Electronic signature appended to the end of this document 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
Ruiz Guiñazú Javier PPD	21-Jul-2021 16:49:22 (GMT)	Document Approval